

PhysiciansCommittee

for Responsible Medicine

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December 9, 2024

Re: Prioritizing Human-Centered Research in the NIH-Wide Strategic Plan;
December 12-13, 2024 Advisory Committee to the Director (ACD) Comment

Sent via email to shawcy@od.nih.gov

Dear Director Bertagnolli and members of the ACD:

On behalf of the Physicians Committee for Responsible Medicine, a 501(c)(3) nonprofit organization supported by nearly one million members and supporters worldwide working for effective, efficient, and ethical medical research and product testing, thank you for the opportunity to comment on this meeting.

The Physicians Committee commends the great progress to advance human-centered research at the NIH, including the acceptance of the recommendations made by the ACD Working Group on NAMs and the launch of the Complement-ARIE program.¹ **To build on this momentum, we recommend that the upcoming NIH-Wide Strategic Plan for Fiscal Years 2026-2030 and its subsequent implementation prioritize human-centered research.** Below, we provide specific recommendations to aid in this effort.² On November 18, 2024, the Physicians Committee and 338 physicians, scientists, and advocates for better human health sent a letter to Director Bertagnolli in support of these recommendations.³

We appreciate your attention to these comments and welcome further dialogue.

Sincerely,

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¹ Statement on catalyzing the development of novel alternative methods, National Institutes of Health, February 1, 2024, Accessed December 9, 2024. <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-catalyzing-development-novel-alternatives-methods>; Complement Animal Research In Experimentation (Complement-ARIE) Program, National Institutes of Health Office of Strategic Coordination-The Common Fund, Accessed December 9, 2024. <https://commonfund.nih.gov/complementarie>.

² 21st Century Cures Act, H.R. 34, 114th Cong (2016).

³ 338 Physicians, Scientists, and Advocates Call on the NIH to Prioritize Human-Centered Research, Physicians Committee for Responsible Medicine, November 18, 2024, Accessed December 9, 2024, <https://www.pcrm.org/news/news-releases/338-physicians-scientists-and-advocates-call-nih-prioritize-human-centered>.

1. Prioritize the development and use of human-centered approaches in the NIH-Wide Strategic Plan for 2026-2030 and coordinate across NIH institutes, centers, and offices.

New approach methods, also sometimes call novel alternative methods or NAMs, are nonanimal methods that can be classified into three categories of technologies: cell-tissue-organoid culture models (*in vitro*), cell-free methods and assays (*in chemico*), and computational modeling and predictive technologies (*in silico*).⁴ In the words of the ACD Working Group on Catalyzing the Development and Use of Novel Alternative Methods to Advance Biomedical Research Working Group, NAMs hold “tremendous promise for helping us better understand fundamental biology to advance human health,” while simultaneously providing potential to reduce or replace the use of animals and to “enable research to be done more quickly, by more researchers, and at a more affordable cost.”⁵ The first funding opportunities from the Complement-ARIE program have been announced, \$18 million per year for NAMs technology development centers and up to \$5 million per year for a NAMs data hub and coordinating center.⁶ The NIH’s continued support for NAMs will improve translation and clinical outcomes, help reduce and replace the use of animals, and increase efficiency of the drug development economy.⁷

To build on this progress and leverage this scientific opportunity, the NIH-Wide Strategic Plan for 2026-2030 should set a formal agency-wide priority to advance the development and use of NAMs and other human-centered research approaches. The NIH-Wide Strategic Plan is a key coordinating and goal-setting document for the agency. It is mandated by Congress to be developed every six years to provide direction to biomedical research, facilitate agency-wide collaboration, leverage scientific opportunity, and advance biomedicine.⁸ The development of the Strategic Plan will soon be underway, offering a vital opportunity to coordinate vision and cooperation across all institutes and centers to further advance the development and use of human-centered research.

⁴ Complement-ARIE Landscape Analysis. NIH Office of Strategic Coordination—The Common Fund. Published August 16, 2024. Accessed December 9, 2024.

⁵ Advisory Committee to the Director Working Group on Catalyzing the Development and Use of Novel Alternative Methods to Advance Biomedical Research. Catalyzing the Development and Use of Novel Alternative Methods. Published online December 2023. https://www.acd.od.nih.gov/documents/presentations/Working_Group_Report.pdf.

⁶ OT-RM-24-015: Notice of Intent to Publish a Funding Opportunity Announcement for Complement-ARIE New Approach Methodologies (NAMs) Data Hub and Coordinating Center (U24 Clinical Trial Optional). Accessed December 9, 2024. <https://grants.nih.gov/grants/guide/notice-files/NOT-RM-24-015.html>; NOT-RM-24-012: Notice of Intent to Publish a Funding Opportunity Announcement for Complement-ARIE New Approach Methodologies (NAMs) Technology Development Centers (UM1 Clinical Trial Optional). Accessed December 9, 2024. <https://grants.nih.gov/grants/guide/notice-files/NOT-RM-24-015.html>

⁷ Ingber DE. Human organs-on-chips for disease modelling, drug development and personalized medicine. *Nat Rev Genet*. Published online March 25, 2022:1-25. <https://www.nature.com/articles/s41576-022-00466-9>; Lucy Meigs et al, “Animal testing and its alternatives—the most important omics is economics,” *ALTEX*. 35, no 3 (July 9, 2018): 275-305, <https://www.altex.org/index.php/altex/article/view/1134>.

⁸ 21st Century Cures Act, H.R. 34, 114th Cong (2016).

2. Ensure that the NIH-Wide Strategic Plan Working Group includes experts in human-centered approaches and that its activities are transparent and accountable.

To develop the NIH-Wide Strategic Plan for Fiscal Years 2021-2025, the NIH Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) established a Working Group made up of representatives from each institute and center and the Office of the Director.⁹ To best harmonize agency-wide efforts for advancing human-centered research, experts in relevant approaches who understand the value of such approaches must be included in and contribute to this Working Group. For example, federal *ex officio* members of the ACD Working Group on NAMs as well as staff from All of Us, the UNITE Initiative, the National Center for Advancing Translational Sciences (NCATS) Tissue Chips Initiatives & Programs, the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, and Complement-ARIE could be called upon for NIH-Wide Strategic Plan Working Group efforts.

Previous Strategic Plans have had limited transparency regarding the prioritization of research. Thus, we recommend that the activities of the Working Group be transparent to promote public accountability and scientific stewardship.

3. Implement comprehensive stakeholder engagement.

Both the NCATS and the Common Fund recently undertook innovative and exemplary strategic planning activities that comprehensively engaged federal and non-federal stakeholders. In preparation for the NCATS Strategic Plan for 2025–2030, NCATS demonstrated open and comprehensive strategic planning, with stakeholder input spanning the earliest stages: first through virtual roundtable discussions, then a request for information on a draft strategic plan framework, and finally a request for feedback on the full draft of the strategic plan.¹⁰ Similarly, the Common Fund hosted a series of listening sessions to gather broad stakeholder input on the goals and structure of the Complement-ARIE Program.¹¹

Exercises like these help institutes, centers, and topical initiatives to understand diverse research perspectives and integrate practical strategies for overcoming barriers and maximizing research impact. We commend the strategies that NCATS and the Common Fund employed and encourage DPCPSI and the NIH-Wide Strategic Plan Working Group to engage in similar efforts to develop the NIH-Wide Strategic Plan for 2026-2030.

⁹ NIH-Wide Strategic Plan. National Institutes of Health (NIH). Published July 30, 2021. Accessed December 9, 2024. <https://www.nih.gov/about-nih/nih-wide-strategic-plan>.

¹⁰ Strategic Plan 2025-2030. NIH National Center for Advancing Translational Sciences. Published September 9, 2024. Accessed December 9, 2024. <https://ncats.nih.gov/about/ncats-overview/strategic-plan>.

¹¹ Executive Summary of the NIH Listening Sessions on the Complement-ARIE Program Concept. National Institutes of Health (NIH). Published March 14, 2024. Accessed December 9, 2024. <https://commonfund.nih.gov/complementarie/strategicplanning/listeningsessions>.

4. Bolster the representation of human-centered expertise in scientific review groups.

A well-recognized phenomenon in peer review is scholarly bias—the favoring of perspectives, theories, or methods that align with one's own.¹² Accordingly, the ACD Working Group on NAMs acknowledged the important role of scientific review in the successful use and deployment of these methods, suggesting that reviewers evaluating projects for potential funding need to appreciate the goals, technology, and usability of NAMs and understand their unique value.¹³

To implement a priority to advance the development and use of NAMs and other human-centered research, the NIH must better equip scientific review groups with human-centered expertise. We recommend broadening the pool of relevant expertise for review groups, including as *ad hoc* reviewers or to provide external input while not officially serving as reviewers. In addition, we recommend allowing individuals from groups other than scientific societies, including nonprofit organizations and industry, to make recommendations through the Reviewer Recommendations Portal.¹⁴

5. Incorporate review criteria related to method suitability, human relevance, translatability, and public health impact in new funding opportunities.

In addition to increasing human-centered expertise, incorporating specific review criteria in new funding opportunities can help ensure that human-centered research projects are fairly and properly evaluated. For example, review criteria should aim to assess methods based on their (a) suitability for the research question, (b) relevance to human biology and disease,¹⁵ and (c) translatability to clinical outcomes,¹⁶ as well as how the project will impact public health.

6. Ensure that human-centered research approaches are not excluded from funding opportunities.

We applaud the supportive steps the NIH has taken to provide human-specific funding streams.¹⁷ However, some recent funding opportunity announcements have explicitly

¹² Langfeldt L, Reymert I, and Svartefoss SM. (2023). Distrust in grant peer review—reasons and remedies. *Sci. Public Policy* 51, 28–41. scad051. https://www.researchgate.net/publication/373303004_Distrust_in_grant_peer_review_-_reasons_and_remedies.

¹³ Advisory Committee to the Director Working Group on Catalyzing the Development and Use of Novel Alternative Methods to Advance Biomedical Research. Catalyzing the Development and Use of Novel Alternative Methods. Published online December 2023. https://www.acd.od.nih.gov/documents/presentations/Working_Group_Report.pdf.

¹⁴ Recommending Potential Reviewers. NIH Center for Scientific Review. Accessed December 9, 2024. <https://public.csr.nih.gov/ForReviewers/BecomeAReviewer/RecommendingPotentialReviewers>.

¹⁵ Leenaars CHC, Kouwenaar C, Stafleu FR, et al. Animal to human translation: a systematic scoping review of reported concordance rates. *J Transl Med*. 2019;17(1):223. <https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-019-1976-2>.

¹⁶ Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Validation Workgroup. Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies. Published online March 2024. Accessed December 9, 2024. https://ntp.niehs.nih.gov/sites/default/files/2024-03/VWG_Report_27Feb2024_FD_508.pdf.

¹⁷ E.g., NOT-RM-24-015: Notice of Intent to Publish a Funding Opportunity Announcement for Complement-ARIE New Approach Methodologies (NAMs) Data Hub and Coordinating Center (U24 Clinical Trial Optional). Accessed December 9, 2024.

called for research approaches that use animals, excluding researchers from proposing projects that use human-centered approaches.¹⁸ Such exclusion limits research, stifles innovation, and perpetuates poorly translatable science. To implement a priority to advance the development and use of NAMs and other human-centered research, the NIH should ensure that these approaches are not excluded from new funding opportunities.

7. Track and report the use of animal- and human-based approaches in funded projects across research areas and other metrics of success.

Transparent and accurate measuring of metrics of success will help gauge progress on goals related to the broader use of human-centered approaches and the replacement of animals, improve public accountability, and ensure scientific stewardship. Such metrics should include the number and percent of awards using NAMs, the number and percent of awards using human subjects, the number and percent of awards using animals (vertebrate and invertebrate), as well as other measures that provide insight into the translatability and impact of biomedical research, like clinical trial success rates.

Some of these measures may only need to be reported annually, but others can be provided consistently, in an up-to-date accounting via the NIH RePORTER database. For example, a simple modification to RePORTER database entries should be made to indicate whether a project involves human subjects or uses vertebrate animals. All that would be required is the incorporation of information pulled directly from the grant application form G.220 – RESEARCH & RELATED Other Project Information. In addition to being tagged in RePORTER entries, this information should be added as search criteria via the “Advanced Search” tool. This would allow the public to easily see detailed spending associated with animal and nonanimal research, improving transparency and promoting accountability while requiring little additional burden for the NIH.

<https://grants.nih.gov/grants/guide/notice-files/NOT-RM-24-015.html>; NOT-RM-24-012: Notice of Intent to Publish a Funding Opportunity Announcement for Complement-ARIE New Approach Methodologies (NAMs) Technology Development Centers (UM1 Clinical Trial Optional). Accessed December 9, 2024. <https://grants.nih.gov/grants/guide/notice-files/NOT-RM-24-012.html>; RFA-AI-24-067: Development of Alternative Human Models of Radiation-Induced Injuries (Extracorporeal Systems) (U01 Clinical Trial Not Allowed). Accessed November 27, 2024. <https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-24-067.html>; PAR-25-198: Engineering Next-Generation Human Nervous System Microphysiological Systems (R01 Clinical Trials Not Allowed). Accessed December 9, 2024. <https://grants.nih.gov/grants/pa-files/PAR-25-198.html>.

¹⁸ E.g., PAR-25-214: Development of Animal Models and Related Biological Materials for Down Syndrome Research. Accessed December 9, 2024, <https://grants.nih.gov/grants/guide/pa-files/PAR-25-214.html>; NOT-AI-24-082: Notice of Special Interest: Establishing and Utilizing Pre-Clinical Animal Models to Study Post-TB Lung Disease Development. December 9, 2024. <https://grants.nih.gov/grants/guide/notice-files/NOT-AI-24-082.html>.