

# PhysiciansCommittee

for Responsible Medicine

PCRM.ORG

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Re: NOT-MH-20-003: Request for Information (RFI) on the 2020 National Institute of Mental Health (NIMH) Strategic Plan for Research

Submitted electronically via [grants.nih.gov/grants/rfi/rfi.cfm?ID=92](https://grants.nih.gov/grants/rfi/rfi.cfm?ID=92)

Dear Joshua A. Gordon, M.D., Ph.D., Director of NIMH,

On behalf of the Physicians Committee for Responsible Medicine, we appreciate the opportunity to comment on the National Institute of Mental Health (NIMH) strategic plan. We strongly support the mission of NIMH to transform the understanding and treatment of mental illness through basic and clinical research, but we urge NIMH to reshape the Strategic Plan for Research in several key areas in order to achieve the Institute's vision of a mental health care future that is truly equitable and responsive to our most vulnerable populations.

We support the four high-level goals in the Strategic Plan and many of the proposed strategies, especially those related to understanding risk and protective factors, determining effective treatment and prevention interventions, and increasing the diversity of study participants, which demonstrate the Institute's willingness to correct research priority deficiencies and better serve communities in need. However, the central goal of Defining Brain Mechanisms remains shackled by the legacy of animal experiments and reductionist paradigms. There are also several missed opportunities for NIMH to position itself as a global leader of health research through forward-thinking policies, research, methods development, and training programs. The following are our recommendations to address these issues and amplify the impact of the Strategic Plan.

- 1. Shift away from the use of animal experiments and expand human-based research.** The Institute's continued support for the use of animals as basic experimental systems to investigate human disease mechanisms fails to recognize the numerous scientific and ethical limitations of such research. Support for such research must be rescinded and replaced with research utilizing human-based experimental systems.
- 2. Prioritize environmental, social, and lifestyle factors research.** Create an independent research goal to investigate environmental influences on mental health such as social factors, environmental exposures, the microbiome, and lifestyle factors such as nutrition.
- 3. Prioritize diversity in research and the workforce and promote diverse research ideas.** The Strategic Plan shows effort in many dimensions to address disparities in the workforce and in research and care, but it fails to make these complex issues central to its goals by not making them a clear, stand-alone priority.
- 4. Increase ethics standards, practices, and training.** Advancements in mental health research must be developed concurrently with the strongest of ethical regulations, guidance, and training. Ethics should be made a priority research area, standards must be strengthened and developed with leadership from diverse stakeholders, especially the public, and training standards must be expanded.

Detailed recommendations follow this page. We sincerely appreciate your attention to these comments and welcome further dialog to ensure their implementation.

Sincerely,

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## **RECOMMENDATION 1. SHIFT AWAY FROM THE USE OF ANIMAL EXPERIMENTS AND EXPAND HUMAN-BASED RESEARCH.**

We applaud recent efforts at NIMH to clarify its position that, “genetically engineered animals should no longer be interpreted as veridical models of psychiatric disorder pathogenesis or pathophysiology” and that human cellular models must be advanced for more effective preclinical neuropsychiatric approaches<sup>1</sup>. From molecules and synapses to circuits and behavior, animal-based experimental systems cannot capture the complex phenotypic presentation of human mental substrates. Aside from the significant inter-species physiological differences at play, animal experiments fail to model psychiatric disorders because they capture neither the extensive polygenicity nor the complex environmental, social, and lifestyle factors associated with psychiatric risk. Furthermore, it is impossible for animal systems to capture human demographic diversity, which must be prioritized in mental health research on the path toward achieving mental health equity, a central tenet of NIMH goals.

The Institute’s recognition of the serious limitations of animal systems must be made more explicit and extend to basic research investigations. We therefore recommend that NIMH make the following changes to the Strategic Plan to reflect its commitment to human-based approaches.

### **A. Request the use of human-based experimental systems for basic research.**

Explicitly state the need for human-based experimental systems in the following sections of the Strategic Plan:

- 1) **Strategy 1.1.A and 1.1.C** (pg. 16, 17): These strategies should state that *human-based systems* should be used rather than leave room for misinterpretation that these research interest areas should be addressed with animal experimental systems.
- 2) **Strategy 1.3.A** (pg. 19): Rectify the ambiguity in neural circuit investigations by explicitly stating that *human* neural circuits and network components should be studied.
- 3) **Strategy 1.3.C, Interest area 3** (pg. 20): The word “animal” should be removed so that the causal nature of circuitry-based hypotheses for mental function and dysfunction are human-relevant and translatable.

### **B. Increase funding for patient-derived and engineered cell culture efforts, post-mortem tissue studies and repositories, and non-animal neurotechnology innovation.**

*NIMH must recognize the need for increased support of these methodological approaches within the Strategic Plan.* Human-based experimental systems are better suited to recapitulate the basic mechanisms of human brain biology than animal-based systems. Cell culture systems can either be derived from patients or genetically modified to contain relevant genetic risk backgrounds and can be used in innovative ways such as in microphysiological systems to study disease mechanisms. Post-mortem tissue from well-characterized individuals can be used to investigate disease mechanisms *in vivo*. Approaches involving human subjects such as epidemiology, genetics and genomics, and imaging can be employed to understand disease mechanisms, especially across the lifespan. To accompany the increase in prioritization for human-based approaches in mental health research, *NIMH must ensure that scientific research officers and study section participants have appropriate expertise* in human-based methodologies. We therefore recommend communicating commitments to expand relevant resources and expertise in scientific review within the Strategic Plan in sections such as “Scientific Stewardship” and those relating to training.

### **C. Clarify support for human-based preclinical research in the Strategic Plan to reflect the Institute's recognition of the poor value of animal-based systems to determine efficacy in mental health interventions.**

We are especially encouraged by the recent statement from the National Advisory Mental Health Council Workgroup on Genomics that, “efficacy against an end-point in an animal cannot be expected to predict

efficacy in humans” and that human cellular models must therefore be advanced for more predictive preclinical neuropsychiatric approaches<sup>1</sup>. Accordingly, we specifically recommend the following changes to the Strategic Plan that clarify support for human-based preclinical research:

- 1) **Strategy 1.3.D** (pg. 20): The development of these interest areas should involve significant support for human-based novel technologies to improve translations to human subjects.
- 2) **Strategy 3.1.A and 3.1.B** (pg. 25): Novel interventions should be developed using human-based experimental systems and animal-based preclinical approaches should be avoided.

Additionally, to correspond with shifts in preclinical strategies to human-based approaches, *NIMH must change application review criteria to ensure evidence in animals is not required to fund in vitro or human clinical studies.*

#### **D. Demonstrate greater transparency by showing funding allocations broken down by human- or animal-based experimental systems.**

In order to demonstrate a commitment to proposed strategies and their implementation, NIMH should provide transparent accounting of the number of projects funded and total funding by type of project. A current snapshot of funding allocations should be included in the Strategic Plan, and subsequent strategic updates should include up-to-date funding allocations and analyses of shifts in funding. This would be in strong alignment with the "Scientific Stewardship" (pg. 3) approaches outlined in the NIMH strategic Plan. These monitoring measures, along with others already collected by NIMH, should be analyzed and made publicly available on an annual basis to enhance scientific rigor and accountability. A good example of these practices can be found in National Plans to Address Alzheimer's Disease<sup>2</sup>.

#### **E. Set a deadline for eliminating animal-based research and develop a roadmap that explicitly prioritizes the reduction and replacement of animal-based research.**

Setting a time-limited commitment to move away from animal-based experimental systems is in line with international ethical principles (e.g. the 3Rs: replacement, reduction, refinement) and would guide researchers in the adoption of more human-relevant approaches. A framework could be adapted from the 2018 roadmap released by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), "A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States<sup>3</sup>." This roadmap is a resource intended to guide U.S. federal agencies and stakeholders seeking to adopt new approaches to safety and risk assessment of chemicals and medical products that improve human relevance and replace or reduce the use of animals. Such an action would also be in line with the Environmental Protection Agency's recent directive to reduce mammal research by 30 percent by 2025 and to eliminate all mammal research by 2035<sup>4</sup>.

An NIMH-led roadmap to replace animals in mental health research would be the first nationwide initiative to do so within the realm of basic biomedical research and would fulfill the Institute's mission to transform our understanding and treatment of mental illness and improve human health.

## **RECOMMENDATION 2. PRIORITIZE ENVIRONMENTAL, SOCIAL, AND LIFESTYLE FACTORS RESEARCH.**

We appreciate the Cross-Cutting Research Theme of "Environmental Influences," which recognizes the multitude of non-genetic factors contributing to mental illness risk. However, the Strategic Plan inadequately prioritizes this large area of research encompassing all the environmental, social, and lifestyle factors associated with mental health and illness. For example, in a hold-over from the era of a genetically-dominant research perspective, Objective 1.2 (pg. 17) states to "Identify the genomic and non-genomic factors associated with mental illnesses," but then fails to present non-genomic strategies and interest areas that

would expand upon important environmental, social, and lifestyle factors that contribute to the mechanisms of mental illness and health. We therefore recommend that NIMH make the following changes to the Strategic Plan to reflect its commitment to such investigations.

#### **A. Create a distinct research objective for environmental, social, and lifestyle investigations.**

Understanding and addressing mental illness requires a multidimensional research lens such as the framework laid out by the National Institute on Minority Health and Health Disparities<sup>5</sup>. This framework includes domains of influence from biological and behavioral factors to physical and sociocultural environments and healthcare systems. If applied to mental health research, it would adequately account for the many determinants of mental health and illness and would encourage the rigorous and creative research thinking necessary for understanding the complexities of mental health and disease. The Strategic Plan does address sociocultural and healthcare factors, but NIMH must do a better job of recognizing and communicating the importance of lifestyle factors such as nutrition and physical activity and their relationship with mental health. We therefore recommend that the Strategic Plan include a distinct research objective that details how to expand such investigations.

Example interest areas include:

- 1) Investigating interactions between the microbiome and mental illness in cross-sectional and longitudinal human studies.
- 2) Elucidating the relationship between mental illness, lifestyle factors, general comorbidities, and mortality (e.g., lifestyle factors and quality of life in people with schizophrenia<sup>6</sup>; mortality from cardiovascular disease in people with severe mental illness<sup>7</sup>).
- 3) Examining the role of diet in mental illness in controlled human trials (e.g., fiber intake and depressive symptoms<sup>8</sup>; plant-based diet and quality of life<sup>9</sup>).
- 4) Conducting large controlled trials and meta-analyses on lifestyle interventions for mental illness.

#### **B. Develop cross-institute initiatives and mechanisms related to mental health and lifestyle research.**

Because lifestyle research encompasses many different aspects of human health including behavior, cardiovascular factors, aging, metabolism, and health disparities, such research should draw on the strength and expertise of multiple NIH institutes. As the Strategic Plan outlines the strength of multi-institutional initiatives to support research in areas of diversity and HIV/AIDS, similar projects should be developed by NIMH and other NIH institutes, centers, and taskforces such as the National Heart, Lung, and Blood Institute, National Institute of Aging, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute on Minority Health and Health Disparities, National Center for Advancing Translational Sciences, and the Nutrition Research Task Force to investigate lifestyle factors in mental health. Whenever possible, NIMH should work with other institutes and centers to align and highlight the synergistic elements of each multi-year strategic plan.

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### **RECOMMENDATION 3. PRIORITIZE DIVERSITY IN RESEARCH AND THE WORKFORCE AND PROMOTE DIVERSE RESEARCH IDEAS.**

We underscore the Institute's commitment to increase research participation from diverse populations in order to understand mental illness pathology in everyone and to ensure that advances in mental health care benefit everyone equitably. Researching mental health in diverse human populations is a necessity in the interrogation of mental health disparities. Diverting resources from the pursuit of this goal to studies of diversity in animals is misguided and harmful as animal experimental systems are unable to recapitulate the diversity of human populations. Furthermore, to avoid exacerbating existing mental health disparities, any strategy that employs human subjects or samples must have a demographic breakdown that is representative of US mental illness

rates. (For an example of how a lack of research subject diversity can exacerbate health disparities, see Martin et al.<sup>10</sup>)

The Institute's prioritization of diversity must be made more explicit and detailed diversity-related strategies must be expanded upon. We therefore recommend that NIMH make the following changes to the Strategic Plan to reflect its commitment to diversity within mental health research.

**A. Create a Cross-Cutting Research Theme section dedicated to diversity to make this important concept a clear priority.**

For an effective and comprehensive research program that integrates diversity, we recommend the following:

- 1) Dramatically increase funding for the development of human-based models, tools, and technologies that must be used to investigate the intersection of demography and mental illness, including *in vitro* and computational approaches. For example:
  - a. Increase outreach efforts to underrepresented communities to encourage organ and tissue donation.
  - b. Fund research to develop human cell populations representing the multifactorial diversity of human patient populations.
  - c. Redirect any funding of the development of "diversity" animal models to studies utilizing diverse human-based samples or human subjects.
  - d. Fund research aimed at developing appropriate methodologies and technologies for improving the handling of analyses of diverse human cohorts.
- 2) Enforce the NIH Inclusion Policy<sup>11</sup> more strictly to ensure non-white subject participation in research studies and extend it to research involving any human biospecimen, including post-mortem tissue and cell-based experimental systems.
- 3) Replace inadequate engagement and protections practices with community-based co-leadership in strategic development. Community engagement must prioritize minimizing risk to research participants and be intentional, culturally sensitive, language appropriate, reciprocal, mutually agreed upon, and evaluated regularly<sup>12,13</sup>.
- 4) Address all aspects of diversity including race, ethnicity, sexual and gender identity, immigration status, socioeconomic status, disability status, and geography.

**B. Avoid the misleading and harmful language of "indiscriminate" mental illness.**

*In the introduction paragraph of "Challenges and Opportunities" (pg. 7), remove the sentence, "Mental illnesses are indiscriminate and cut across gender, age, race, ethnicity, and socioeconomic status." While we understand the sentiment of this wording, we believe it accomplishes the opposite of what it intends to. Instead of highlighting that anyone can be affected by mental illness, this sentence erases the very real discriminatory nature of mental illness rates across demographics. For example, men, American Indian and Alaska Natives, and people living in rural areas experience higher rates of suicide<sup>14</sup>, women and youth experience higher rates of any mental illness<sup>15</sup>, low household income is associated with mental illness and suicide<sup>16</sup>, and people of color are less likely to receive the mental health care they need<sup>17</sup>.*

**C. Expand intramural and extramural workforce diversity efforts.**

We support the Strategic Plan's cross-cutting theme of investing in a well-trained diverse workforce. This is not only the right thing to do, but it ensures a diversity of perspective that is necessary for optimal discovery and innovation. For example, emphasis should be placed on research that departs from the "first in animals" preclinical model and researchers that are seeking ways to more relevantly study diversity in preclinical studies using human-based approaches. In addition, by departing from reductive, animal-based mechanistic studies, diversity in scientific perspectives would increase the number of much needed studies on social, environmental, and lifestyle risk factors in human-based model systems.

We also urge NIMH to explore and address reasons for low award rates in non-white investigators, for example, by more heavily prioritizing research involving human subjects and using human samples and studies investigating health disparities and patient-focused interventions<sup>18,19</sup>. Furthermore, NIMH should expand workforce diversity measures beyond awarding, hiring, admissions processes. *Retention of marginalized trainees and PIs must be prioritized*, for example, through improvement to their material conditions such as through higher wages and protections against discrimination and harassment. NIMH must lead by example by putting these measures into place intramurally and it must incentivize extramural institutions to follow suit through training and award mechanisms. Finally, we encourage NIMH to *invest in neurodivergent and mentally ill researchers* who bring the invaluable perspective of lived experience to the Institute's mission.

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#### **RECOMMENDATION 4. INCREASE ETHICS STANDARDS, PRACTICES, AND TRAINING.**

*“Science sans conscience n'est que ruine de l'âme;” science without conscience is the ruin of the soul.*<sup>20</sup> – François Rabelais

The U.S. biomedical research enterprise has consistently failed to perform the most basic ethical analyses in conjunction with research planning and conduct, a fact that is exemplified by the continued use of animal experimental systems despite decades of failure and wasted resources<sup>21,22</sup>, by the systematic exclusion of women from clinical trials<sup>23</sup>, and by the systematic exclusion of non-white participants from genome-wide association studies<sup>24</sup>. We are past due for bringing conscientiousness back into the practice of science. *NIMH must make an explicit commitment to ethics, a word that is not even mentioned once in the Strategic Plan.* A Strategic Plan that does not discuss an interconnected development of ethical guidelines, regulations, and protections demonstrates a severely flawed approach to scientific discovery and therapeutic development. We therefore recommend that NIMH state such a commitment to ethics under the "Scientific Stewardship" section and make the following changes to the Strategic Plan to reflect its commitment to the ethical conduct of mental health research. Although these recommendations may be included as parts of Cross Cutting Themes, it would be far more impactful if they were included as a fifth goal of the strategic plan.

##### **A. Establish an NIMH Ethical, Legal and Social Implications program.**

*In order to comprehensively address new and persistent ethical, legal, and social implications (ELSI) related to advances in mental health research, it is imperative that NIMH establish an ELSI program.* Importantly, this would pave the way for other institutes to do so as well on the path toward a much-needed NIH-wide ELSI program or an expansion of the Department of Bioethics beyond the activities of the Clinical Center. The National Human Genome Research Institute is the only NIH institute with an ELSI program, but human genome research is not the only realm of biomedicine warranting such a special effort<sup>25</sup>.

As brain data such as electroencephalograms and imaging become more advanced, opportunities for subject reidentification and discrimination increase, thereby increasing risk for research participants. Furthermore, protections to subject data and biospecimens must not be superseded by other agencies or corporations for non-research or malicious purposes (e.g., security, immigration). Individuals with mental illness already face stigma and discrimination, and their protection within a research context must be a priority. Formal plans for the replacement of animal experimentation with human-based approaches and understanding implicit and explicit bias that prevent the objective evaluation of research methods failures are just some of the many aspects of research ethics that must be addressed by NIMH. A dedicated ELSI program would ensure that a comprehensive ethical view is taken regarding mental health research.

##### **B. Increase ethics standards and practices.**

1) *Increase ethics standards and implement more widespread and rigorous ethics practices and to include clear commitments to this in the Strategic Plan.* For example, while we are encouraged by the Management

and Accountability section regarding Enhancing Risk Management (pg. 5), we believe current risk assessments are applied too sparingly and that thorough harm-benefit analyses should be performed for every project proposal. Such a large-scale effort would require dedicated staff with ethical expertise acting in conjunction with scientific review officers and program officers.

2) *Form strategic plans and research policies with leadership from more ethicists and particularly from stakeholders with divergent interests and ethical views.* Ethics standards must be developed in conjunction with communities, particularly with animal protection groups, patient advocacy groups, and advocates for especially at-risk populations like individuals with severe mental illness. For NIMH to carry out its mission, it is imperative that it listen to the needs and warning cries of these groups. For example, the autism community remains wary of autism genetics research because of thoughtless or imprecise language that the purpose of such research is to eradicate the condition<sup>26</sup>. This measure goes beyond engagement based on improving communication and understanding of the Institute's values by showing a willingness to revise and evolve perspectives and practices and drawing on the experiential expertise of these stakeholder groups.

### **C. Increase ethics training standards.**

A well-trained workforce should be able to do more than design experiments and synthesize results – it must be able to anticipate and evaluate the ethical and social implications of research. However, as previously mentioned, various ethical failures on the part of the U.S. biomedical research enterprise are exemplary of the lack of rigorous ethics standards. We believe one reason for this is that biomedical ethics training is severely lacking<sup>27</sup>. Ethics training courses narrowly focus on human subject protections and research misconduct while avoiding the more difficult discussions of animal experimentation, systemic scientific attitudes that avoid responsibility for the harms caused by experimentation, and disseminating scientific knowledge isolated from direct societal impact. *We therefore propose that NIMH establish increased ethics training standards within training and early stage investigator mechanisms to ensure an ethically responsible future of mental health research.* We propose a full year (two semesters or three quarters) of rigorous ethics coursework within doctoral and postdoctoral training programs and we propose ethical research design components in studies that promote ethical protections and work towards the replacement of animal use in mental health research.

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