October 27, 2023

The Honorable Bill Cassidy, M.D.
Ranking Member
Committee on Health, Education, Labor and Pensions
United States Senate
428 Dirksen Senate Office Building
Washington, DC 20510

Dear Ranking Member Cassidy:

On behalf of Cincinnati Children's, I am pleased to submit the following response to your request for stakeholder input regarding modernization of the National Institutes of Health. Earlier this year, we were honored and humbled to be named the top children's hospital in the nation by *U.S. News & World Report*. A critical mission has been research to achieve the scientific breakthroughs that will bring about improved prevention and health promotion interventions, safe and effective treatments, and even cures for the diseases of childhood. Transformative discoveries achieved in the laboratories of Cincinnati Children's include the oral polio vaccine, the rotavirus vaccine, the first heart-lung machine and artificial surfactant to develop the lungs of babies born prematurely.

Research shows that child health sets the foundation of health in adulthood. Prevalent adult conditions such as heart disease, diabetes and mental health have their origins in childhood, with the most effective prevention starting prenatally and in pediatrics. The genomic revolution offers the promise of prediction, pre-emption and precision medicine, pushing identification and intervention earlier in the disease and life course as we have the capacity to know the whole genome of a fetus. Advancing science in artificial intelligence prediction and social determinants of health emphasizes the potential of earlier identification, prevention and health promotion. Research early in the life course offers the best hope to intervene and improve societal health.

Perhaps the most significant resource to drive advancements in medicine at Cincinnati Children's and throughout the nation is NIH funding. Cincinnati Children's has long been among the top two or three children's hospital or pediatric department recipients of NIH funding, with grants spanning all NIH Institutes and Centers (I/Cs). As such, we have a vested interest in an NIH that is well-resourced and optimally structured. It is our hope that any efforts to modernize the NIH recognize the immense value of this resource to the nation and the world and that efforts be focused on strengthening and refining its operations. With that orientation, we are pleased to offer the following ideas for your consideration.

Increasing the Pace of Science

In your view, what would be the appropriate balance between basic, translational, and clinical research at NIH? How can NIH continue to prioritize truly fundamental research while improving outcomes for translational and clinical projects?

NIH must support research activity in all three of these categories as medical research is a continuum. NIH must always have basic research at its core as this fundamental and early-stage research activity is often not of imminent interest to other stakeholders, such as the biopharmaceutical industry, given the nature of the research and the many years (or decades) that are between basic discoveries and translation into a potential intervention being evaluated for use in humans. But NIH also has an important role to play in bridging the transition from basic and translational/clinical, particularly in fields like pediatrics where we often have very small patient populations and thus very limited biopharmaceutical industry interests.

What lessons can be learned from individual NIH Institutes and Centers (ICs) related to the conduct of clinical research? How can clinical trials be conducted more efficiently and effectively? What types of trials should NIH conduct, and what types are more appropriate for industry to undertake?

Building upon the previous points, NIH has an important role to play in supporting targeted clinical research activities, particularly in fields like pediatrics since most diseases of childhood are, thankfully, rare. This means that while a single study site may be sufficient for an adequately powered study of a prevalent adult-onset disease, pediatric clinical trials almost always need to include multiple sites to enroll an adequate number of patients. Involving multiple centers typically means a greater cost, particularly if measured at the per-capita level in studies that involve rare or very rare pediatric conditions.

It's also important to note that these trials must ensure representation of the overall patient population impacted by a disease or condition. This means we cannot be limited exclusively to the largest children's hospitals or academic centers and need trial sites in mid and smaller research settings through a hub-and-spoke model. NIH has recognized the need to strengthen pediatric clinical trial capacity by establishing the IDeA States Pediatric Clinical Trials Network. We encourage Congress and the NIH to take additional actions to support the development of pediatric trial capabilities.

We strongly advocate that pediatric populations never be excluded from research simply because recruiting them may be more costly or burdensome than adult populations. We remain concerned that more than five years into recruitment, the *All of Us* Precision Medicine program has yet to enroll a single child, though we are pleased that a pediatric director was hired in late 2022. We understand the need to protect children who participate in research programs, but believe we cannot accept delays simply because this work is more complicated when children are included.

Extramural Research & Programs

How do academic institutions typically fund the salaries of extramural investigators? What benefits and challenges come with this approach? How could this practice be reformed to better support the biomedical research workforce and ensure that NIH dollars, on a per-project basis, accurately reflect the time commitments of each investigator and staff member?

Cincinnati Children's funds investigator salaries using a mix of NIH funding and institutional support. Because of NIH salary caps and budgetary limits on grant awards, investigator effort on individual projects is heavily subsidized by the institution. Congress must recognize the significant and growing financial commitments to medical research made by institutions like ours. An Association of American Medical Colleges survey found that for every $1 in grant funding, institutions contribute 53 cents on average. Cincinnati Children's is fortunate to have a vibrant research foundation to support our activities, but many institutions are not so well-situated. The other source of funding is clinical margins. Given the heavy reliance of most children's hospitals on Medicaid, we are disadvantaged compared to non-pediatric institutions that have a more diverse payer mix.

We are also concerned by the difficulties we and our peer children's hospitals and academic departments have encountered in competing within the larger NIH research ecosystem. This includes instances in which children's hospitals cannot apply when eligibility is only for degree-conferring institutions, or when there is only one award per institution because pediatric departments in adult medicine-dominated institutions are disadvantaged. We urge that any NIH modernization effort address this problem by ensuring inclusion of all segments of the lifespan in NIH initiatives, particularly signature initiatives, unless there is a scientific rationale for their exclusion.

We further recommend that NIH consider ways to address the need for directly supporting pediatric research within each of its institutes and centers. It is reasonable to expect or even require that a percentage of the total meritorious awards for NIH initiatives be focused on child health research programs. Ultimately, we need lawmakers and the NIH to recognize the reality that most adult-onset diseases have their roots in the pediatric years, and that research in child health is necessary to understand both the etiology of diseases as well as potential strategies to treat and prevent onset of disease.

What specific factors cause individuals to leave the biomedical research workforce? How could common NIH funding mechanisms be revised to better recruit and retain high-quality investigators, including young investigators?

A recent report by the National Academies of Science, Engineering and Medicine (NASEM) entitled "The Future Pediatric Subspecialty Physician Workforce: Meeting the Needs of Infants, Children, and Adolescents" articulated the myriad challenges to the pediatric research workforce, dedicating an entire chapter to this issue. These include lengthy and costly training, limited mentorship and training opportunities, clinical demands and lower clinical margins in pediatrics, and inadequate time protected for research activities. As the NASEM study states, across all disciplines, the numbers of physician-scientists have diminished, and the length of their productive scientific careers has decreased, with the average age of first independent funding at 46 years old. That is a 10-year drop from the 1990s when the average age of first independent funding was 36 years old.

The NASEM report recommended that the NIH "should increase the number of career development grants in pediatrics, particularly institutional training awards, the Pediatric Loan Repayment Program, and K awards with attention to providing such grants to physician-scientists from backgrounds that are underrepresented in the scientific workforce and for high-priority subspecialists in pediatric research." The recommendation also calls for K award funds to "reflect current salaries" and for such awards to also include the costs needed to obtain mentorships.

We strongly agree with this recommendation and would urge that Congress include it within any NIH modernization legislation. We note that we strongly support a pending bipartisan bill sponsored by Sens. Ernst and Coons and Reps. Joyce and Schrier, the Pediatricians Accelerate Childhood Therapies Act, that would establish an NIH-wide pediatric research award program that speaks to this recommendation.

Instead of seeking to cap awards, a proposal NIH put forward but promptly retracted several years ago, we would instead focus on strengthening K and other training awards as proposed in the PACT Act to ensure young investigators have the support needed to move toward and eventually become independent investigators. We also encourage NIH to explore ways to make the K-to-R transition, which the NASEM report described as being "tortuous and prolonged," less burdensome.

Statutory Structure and Functions

How might NIH's mission, strategic goals, and objectives be refined to better reflect and enable its core function?

Per our opening comments, Cincinnati Children's strongly supports the mission and goals of the NIH, including NIH's traditional focus on basic research. We do think NIH should regularly revisit, through a transparent process, the process by which it sets research priorities, and encourage that Congress and NIH ensure any such efforts recognize the importance of maintaining a vibrant research portfolio across the lifespan that includes child health. We also reiterate that a robust focus on pediatric research not only benefits children but also adults, given the growing body of research that adult health and well-being or, conversely, poor health are often rooted in the early years of life. By ensuring an adequate focus on lifespan and pediatric research, NIH will support research to understand these antecedents.

Could NIH research dollars be better allocated within the agency's portfolio? Are there certain areas of research that are over-funded or under-funded? What strategy should Congress and NIH take in allocating resources to specific areas?

It is essential that NIH's funding decisions and priorities are always informed by science. We believe that NIH in general has operated in an open and transparent manner and uses science appropriately to drive its priorities. Any modernization efforts should seek to clarify the process NIH uses to establish and regularly revisit its funding priorities. As a children's hospital research institute, however, we have sometimes been challenged by NIH initiatives that have inadequately focused on child health needs. For example, the *All of Us* Precision Medicine Initiative has yet to move forward with a child recruitment program more than five years after beginning mass enrollment, and the Clinical and Translational Science Awards (CTSAs) have included a very limited focus on pediatrics at most sites.

In making such decisions, NIH must not simply focus on numbers of people impacted by a disease or diseases. Doing so places those impacted by rare diseases at a disadvantage and would include children since most diseases of childhood are rare. Priority-setting must continue to include multiple criteria beyond prevalence of a disease, including the impact of a disease or diseases on quality of life as well as the scientific opportunity before us. We would suggest an NIH process that formally defines rare disease, not only broadly but also in childhood.

How could NIH better prioritize its programs to support core activities, reduce redundancy across its ICs, and ensure activities are appropriately targeted?

Because child health research cuts across all or almost all Institutes and Centers, an opportunity exists to help better coordinate and prioritize this activity. NIH launched the NIH Pediatric Research Consortium (N-PeRC) more than five years ago to better support pediatric research programs across Institutes and Centers. However, from our perspective, very few tangible initiatives benefiting child health have resulted from this consortium to date. We believe N-PeRC could be strengthened through the following actions:

- Codify N-PeRC into statute so that it is enshrined in permanent law.
- Require regular reporting on key metrics, including specific projects supported or expanded.
- Add an external advisory component so that the NIH is hearing not just from intramural leaders, but from its external stakeholders and key constituents, including children's hospitals and research institutions.
- Consider extending N-PeRC so that there is an Office of Child Health Research located within the Office of the Director (OD) tasked with leading the development and execution of an NIH-wide pediatric research strategy.

Administrative Opportunities & Challenges

Regarding NIH's interagency collaborations, what currently works well and what could be improved? How can NIH better leverage capabilities that exist within the interagency, particularly for technologies and disciplines outside NIH's traditional scope?

What opportunities exist to harmonize funding applications for research awards across ICs and the interagency?

One important area of opportunity is NIH's interactions with the Food and Drug Administration (FDA). For example, opportunities abound for collaboration between the two agencies to support the development and approval of products to treat rare pediatric conditions. Leveraging disease registries, including those supported by the Centers for Disease Control and Prevention (CDC) and/or housed at institutions like ours, can provide the data necessary to inform regulatory reviews, including post-approval or confirmatory studies.

What impact would capping the number of concurrent awards for a principal investigator have on the output of NIH's extramural investments?

We do not believe capping awards to PIs will have a positive impact. While we understand the desire to support early-career researchers, a topic we are passionately committed to and spoke about in a prior section, capping awards of successful PIs will ultimately inhibit science and risk sending high-performing researchers out of the NIH ecosystem. The optimal path toward attracting and retaining younger scientists requires providing more robust support as well as helping to facilitate and shorten the transition to independent investigators, points we will speak to more fully.

Improving Transparency & Oversight

What specific policy recommendations do you have to improve the transparency of NIH's work, including its accountability to the American people and Congress? Are you aware of any specific mechanisms that have effectively achieved this goal for other federal agencies, including outside of HHS?

We believe the need and opportunity exist to streamline the bureaucracy associated with NIH awards without negatively impacting transparency in any way. NIH processes need to reflect advancements in technology and should seek to make it easier, for example, for researchers to propose amendments to projects, and by preventing submission of redundant or duplicative information, such as complex data submission plans. Additionally, we believe there may be a need to revisit how research awards are catalogued and tagged so that the data in the Research, Condition, and Disease Categories (RCDC) database is as accurate as possible and reflects the true amounts spent on a disease state or condition during the fiscal year.

What is your view of NIH's current practices of conducting audits of its intramural and extramural programs? How, if at all, could this be enhanced?

Overall, we believe the intramural review program is robust and thorough. We do recommend that consideration be given to including more external reviewer panels with industry given the success of the pilot programs.

Conclusion

Thank you for undertaking this request for information and for your current and longstanding interests in a robust NIH. We hope these comments are useful to you and your staff. If you have any follow-up questions or if you would like to discuss any of these thoughts in greater detail, please reach out to Melissa.Saladonis@cchmc.org or me as we would be pleased to set up a meeting.

Sincerely,

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