PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

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Francis S. Collins, MD, PhD
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892-7985

RE: National Institutes of Health (NIH) Office of Science Policy (OSP) Recombinant or Synthetic Nucleic Acid Research: Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) (83 Federal Register 41082)

Dear Dr. Collins:

Public Responsibility in Medicine and Research (PRIM&R) appreciates the opportunity to comment on the National Institutes of Health (NIH)'s Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines), published August 16, 2018.

PRIM&R is a nonprofit organization dedicated to advancing the highest ethical standards in the conduct of research. Since 1974, PRIM&R has served as a professional home and trusted thought leader for the research protections community, including members and staff of human research protection programs and institutional review boards (IRBs), investigators, and their institutions. Through educational programming, professional development opportunities, and public policy initiatives, PRIM&R seeks to ensure that all stakeholders in the research enterprise understand the central importance of ethics to the advancement of science.

According to the NIH Notice and the August 2018 *New England Journal of Medicine* (*NEJM*) Perspective article, "The Next Phase of Human Gene-Therapy Oversight," by you and Food and Drug Administration (FDA) Commissioner Scott Gottlieb, the goal of the proposed changes to the NIH Guidelines is to streamline oversight of human gene transfer research (HGT), since it "no longer requires special oversight

that falls outside of our existing framework for ensuring safety."[1] The proposed revisions seek to "reduce the duplicative oversight burden" associated with the submission and reporting requirements of the FDA and the NIH, and with overlapping review requirements among the FDA, IRBs, and institutional biosafety committees (IBCs).[2]

PRIM&R appreciates the agency's efforts to reduce duplicative oversight as gene therapy research becomes more routine. We have previously, in other comments submitted to regulatory agencies, indicated our support for eliminating redundant requirements when they add little to the protection of human research subjects. We therefore welcome the proposed modification to make IBC review of HGT protocols consistent with their review of other research that requires biosafety review, and agree that IBCs should remain focused on biosafety. We also agree it is worth reviewing Appendix M to determine whether the requirements for NIH protocol registration submission and reporting overlap unnecessarily with requirements for submission and reporting to IRBs and to the FDA.

However, PRIM&R has serious reservations about the proposed changes to the mandate, purpose, and scope of the Recombinant DNA Advisory Committee (RAC).

Our concerns can be summarized as follows.

- The RAC was established in 1974 to address both known and unknown risks presented by new technologies. Today, human gene therapy technology continues to evolve, and some cases—such as the ability to affect the germline—raise new and even thornier ethical issues. The unique role played by the RAC as originally conceived is at least as essential now as it was 45 years ago.

- In proposing to scale back the role of the RAC, the proposed Guidelines fail to recognize how the RAC's independence, special expertise, and transparency make it uniquely positioned to identify, consider, and address ethical and social implications of the newest genetic technologies and foster public understanding of, and trust in, emerging genetic science.

- The Guidelines propose to remove the RAC's protocol review authority and make it solely an advisory committee. However, discussions in the abstract are no substitute for discussions grounded in review of actual protocols. Having a specific context is very helpful—and sometimes essential—in order to adequately address the complex and as-yet-unresolved ethical challenges raised by rapidly evolving technologies.

- Without more information about the future RAC's composition, responsibilities, and how and when it will be consulted on emerging technologies, it is not possible to

[1] Francis S. Collins and Scott Gottlieb. "The Next Phase of Human Gene-Therapy Oversight." *The New England Journal of Medicine,* 379, no. 15 (2018): 3. doi: 10.1056/NEJMp1810628.
[2] Ibid.

evaluate how much of the current value of the RAC will be preserved under its new mandate.

We expand on each of these concerns below.

The RAC was established to advise the NIH director on whether particular research studies using recombinant DNA technologies should be allowed to proceed, given the potential for misuse and other risks, and to address public anxiety about the significance of these emerging biotechnologies. Since its inception in 1974, the RAC has evolved along with science and public attitudes, and it has continued to play a crucial role in oversight of gene transfer research. The current NIH Guidelines codify the RAC as an independent, transparent, and expert body that both reviews exceptional HGT protocols and provides advice and guidance to the NIH about the conduct and oversight of recombinant DNA technology. These Guidelines require that the proceedings of such meetings typically be open to the public. The new proposal eliminates the RAC's protocol review authority, uses the RAC solely as an advisory committee, and modifies its charter to "change its focus from research solely involving recombinant or synthetic nucleic acids to emerging biotechnologies research." All references to the RAC, and its purpose, scope, and membership are eliminated from the proposed NIH Guidelines. PRIM&R believes this is a mistake, for several reasons.

The first reason for our objection has to do with eliminating the benefits associated with the current public nature of the RAC and the transparency of its work. The RAC is chartered under the Federal Advisory Committee Act, which places special emphasis on open meetings and transparency. As such, the RAC is required to do its work in public, in contrast to IRBs and IBCs, which conduct their reviews of protocols behind closed institutional doors. **The RAC therefore provides a unique forum for the public to witness and participate in discussions about the ethical, societal, and safety implications of HGT research.** In the *NEJM* Perspective article, you and Dr. Gottlieb state that the risks of HGT research should no longer be seen as unique or unpredictable, and therefore the additional oversight added by RAC review is unnecessary. Leaving aside the premise of this argument (with which we disagree below), we believe this misses the point regarding the value of the RAC as it currently operates. Public discussion, deliberation, and debate about the implications of HGT foster public understanding of and trust in emerging science such as CRISPR. Indeed, the NIH itself notes in its current policy that such public review not only promotes the safe and ethical conduct of experiments in this field, it also informs the public about why these studies are significant. **Support and trust from the public are essential for the successful advancement of new technologies, and the role of the RAC is especially invaluable in facilitating public acceptance of an area of science such as human gene transfer**.

Furthermore, since 2000, publicly available review of protocols by the RAC takes place prior to review by IRBs and IBCs.[3] This has two benefits. First, RAC review provides an opportunity for identification of, and deliberation about, whether certain types of human subjects research—for instance, research on germline editing—should be initiated in the first place. **IRBs and IBCs are not well positioned or structured to make such high level policy determinations that affect a general area of research**. Second, because some RAC members have a very high level of expertise in relevant scientific fields such as molecular genetics and recombinant DNA research, **RAC review can serve as an important complement to local IRB and IBC review and shape ongoing review of human subjects research.**

Relatedly, PRIM&R is concerned about the proposed elimination of Appendix L of the NIH Guidelines, Gene Therapy Policy Conferences (GTPCs). The GTPCs serve an important function similar to the RAC, in that these meetings seek to "enhance the depth and value of public discussion relevant to scientific, safety, social, and ethical implications of gene therapy research" by bringing together a broad group of stakeholders. Importantly, proposals for GTPCs may come from the public, including from patient and consumer advocacy organizations, and all GTPC findings are made public. As gene therapy research continues to become more prevalent, and new domains (such as germline manipulation, gene editing, and debates about using these technologies for human enhancement) come to the fore, eliminating these additional opportunities for public discussion of novel scientific issues, their application to human health and the environment, and their societal implications, is of significant ethical concern.

Our second concern regarding the proposed Guidelines is that they fail to recognize the importance of the RAC's independence. As a federal advisory body, composed of national experts from a variety of scientific, public health, and other fields, **the RAC plays an essential role as an oversight entity that is independent from institutions and industries that conduct and support research**. IRBs and IBCs are typically associated with institutions; and the FDA frequently cites concerns about industry's proprietary interests as a reason for not making more deliberations public. The ability of the RAC to conduct an independent, objective, and transparent review of the goals, justification, and risks associated with a research protocol, is invaluable.[4] **The RAC's primary responsibility is to the public, and its primary interest is the public good.**

Given these first two concerns, we believe **it is imperative that the NIH continue to use the RAC as a *public* forum as required by its establishment under the Federal**

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[3] Institute of Medicine, *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee* (2014), 46, https://www.nap.edu/catalog/18577/oversight-and-review-of-clinical-gene-transfer-protocols-assessing-the.

[4] Levine, Carol, Ruth Faden, Christine Grady, Dale Hammerschmidt, Lisa Eckenwiler, and Jeremy Sugarman. "'Special Scrutiny': A Targeted Form of Research Protocol Review." *Annals of Internal Medicine* 140, no.3 (2004): 220-223.

Advisory Committee Act. The NIH should at the very least preserve current procedural policies[5] that representatives of federal agencies shall serve on the RAC, but in a non-voting capacity, and that there be regularly scheduled meetings that are open to the public unless confidential information is involved.[6] The NIH should also retain the existing policy that, should researchers or sponsors wish to prevent the release of information due to proprietary concerns, the burden should be on the applicant to offer a detailed justification for why this is necessary, particularly given the ethical concerns at stake. [7]

Our third concern is that while the NIH proposes that the reconfigured RAC continue to provide advice on biosafety issues related to HGTs upon request, **we predict this more limited advisory role will not have the same impact and value as its oversight and protocol review role.** It is true that in its most recent incarnation, only a small number of protocols have been deemed by the NIH to merit RAC review. This seems appropriate, as the types of recombinant DNA research with which the RAC was originally concerned become more common, and its risks more familiar. However, we believe that in select circumstances, review of protocols continues to be the best means for identifying important ethical issues that may emerge from a particular application of HGT technology. The unique perspective, obtained only when the review takes place at a detailed, "in the weeds" level, is one of the key advantages of the current role of the RAC. The RAC is positioned to use review of protocols (both individual and as a body of cases) to define and differentiate common risks from those that present new, evolving challenges and warrant additional review. **A more general advisory role, without the element of deliberation over particular methodological, technological, or ethical matters associated with specific protocols, is insufficient at a time when rapidly evolving technology is creating new ethical frontiers.**

Furthermore, while some gene transfer applications may now be routine and not candidates for RAC review, **we believe there is actually a *growing* mandate to address the ethical challenges presented by novel forms of genetic modification (such as germline gene therapy and enhancement). Thus we do not agree with the NIH and FDA leaderships' claim that there is no longer any reason for special oversight of HGT research, outside of the existing regulatory framework, for ensuring safety of research participants.** The RAC, as it has been configured, is well suited to address this mandate, since it provides an example of what some have called "special scrutiny" review above and beyond that provided by the standard ethical and regulatory framework for research that raises "serious moral challenges."[8]

In 2017, the National Academies of Sciences, Engineering, and Medicine (NASEM) Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations

[5] Per Section IV-C-2 of the current NIH Guidelines.
[6] Per the language in Appendix M-I-B.
[7] Ibid.
[8] Levine, supra note 4 at 220.

published a report following a multifaceted study of the clinical, ethical, legal and social implications of human gene editing.[9] The committee concluded that while oversight of HGT in basic research and somatic therapies is adequate to ensure public safety, many questions remain concerning, for example, hereditable genome editing. Development of treatments to cure a patient affected with disease or disability is an ethically clear undertaking, but when those processes involve heritable germline alterations, or modifications in fetal cells or *in utero*, the ethical principles and ramifications are considerably more complicated. Furthermore, future applications of HGT technologies designed to enhance the physical and psychological aspects of people not suffering from disease raise fundamental and complex ethical quandaries that must be considered by an open and transparent body.

The NASEM report states that in order to evaluate these larger moral questions, "an expansion of current modes of public engagement will be necessary to help regulatory bodies define and demarcate the boundaries between such terms as "therapy" and "enhancement," or "disease" and "disability.""[10] Protocols proposing experiments to create "genetic alterations that are insufficiently justified, too risky, or too socially disruptive to be pursued at this time"[11] are perfect candidates for special scrutiny by an expert oversight body such as the RAC. In contrast to the Institute of Medicine (IOM)'s 2014 recommendation that the RAC's role be limited, the NASEM 2017 report asserts that HGT research continues to raise serious moral challenges and present novel applications that cannot be anticipated. **Maintaining the role of the RAC in reviewing protocols that represent new scientific advances in HGT is essential for monitoring public discomfort and generating public trust in the advancement of research that carries great promise for human health, but which may take place in highly-charged settings such as the germline.**

The proposal states that the NIH "recognizes the value of the RAC in discussions of science, safety, and ethics," and would like to use the RAC as a "public forum to advise on issues associated with emerging technologies" beyond HGT, including technologies such as gene editing, neuroethology, and synthetic biology. This would also allow the NIH to continue to seek advice from the RAC on biosafety issues associated with HGT research. The preamble to the NIH Notice states a new charter for the RAC is forthcoming. **But without any mention of the future RAC's composition, responsibilities, and how and when it will be consulted, it is not clear how much of the current value of the RAC, or the GTPCs, this new approach will preserve. Before proceeding with the proposed changes in scope and purpose of the RAC, more information is needed.**

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[9] National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance* (2017), https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance.
[10] Ibid., 176.
[11] Ibid., 181.

Ultimately, PRIM&R believes transparency from the federal government on research with emerging biotechnologies is crucial given the safety, scientific, societal, and ethical implications involved. **As the NIH considers updating the NIH Guidelines, we urge it to keep in mind how it can foster a more open environment with respect to deliberations on research with important social implications**. Transparency is particularly important given that key experimental details are sequestered far too often due to sponsors' proprietary concerns. Although HGT research is far more advanced than when the RAC was established, novel HGT technologies and applications are emerging faster than ever. It's worth remembering that in 1999, shortly after the RAC's review function was relaxed, Jesse Gelsinger died in a gene therapy trial. The IOM 2014 report on the oversight of gene transfer research notes that subsequent investigations of Gelsinger's death "identified shortcomings in trial oversight and transparency" specifically related to what information was shared with the RAC.[12] Subsequently, the NIH enhanced the role of the RAC by shifting the timing of RAC public review, and expanding RAC responsibilities. Then, as now, the rapid expansion of human gene transfer research is outpacing the ability of local IRBs and IBCs to foresee the implications and risks for human subjects and for society. **This is not the time to remove the RAC as a mechanism for ensuring appropriate expert review and for keeping the public welfare at the forefront of regulatory oversight.**

Thank you for the opportunity to comment on this important issue. My PRIM&R colleagues and I are available to discuss our comments further, should that be of interest. Please feel free to contact me at 617.303.1872 or ehurley@primr.org.

Respectfully submitted,

Elisa A. Hurley, PhD
Executive Director

cc: PRIM&R Public Policy Committee, PRIM&R Board of Directors

[12] Institute of Medicine, supra note 3, at 46.