



October 10, 2018

Jessica Tucker, Ph.D.
Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, Maryland 20892-7985

Re: Recombinant or Synthetic Nucleic Acid Research: Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

Dear Dr. Tucker,

The Association of American Medical Colleges (AAMC), Association of American Universities (AAU), Association of Public and Land-grant Universities (APLU), and Council on Governmental Relations (COGR), collectively the “Associations,” write in response to Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. We appreciate the agency’s efforts to streamline oversight and eliminate duplicative reporting for human gene transfer (HGT) clinical research and focus the NIH Guidelines more specifically on biosafety issues. We agree with the overall intent of the proposed changes. In this context, we offer the following specific comments and recommendations:

Proposed Changes to Appendix M

Among the possible changes to the NIH Guidelines, on page 41093 of the Federal Register notice, the agency proposes to delete, in its entirety, Appendix M, *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant or Synthetic Nucleic Acid Molecules into One or More Human Participants*. Member institutions have suggested that current guidance on what constitutes a biosafety review of HGT research is limited and that the risk assessment content of Appendix M needs to be preserved by the Office of Science Policy (OSP) to provide a framework for institutional biosafety committees (IBCs). Removal of Appendix M in its entirety leaves the expectations of IBCs unclear in a number of areas. For example, it may result in insufficient information regarding the nature of the recombinant DNA, the vector system (if applicable), and the manufacturing method, for the IBC to be able to adequately assess biosafety. If Appendix M is removed, there should be guidance/instructions to study sponsors regarding what specific information needs to be presented elsewhere in the study documents for a reasonable assessment of biosafety.

Recommendations:

- We recommend adapting Appendix M-1-A (4; a-f) as guidance for HGT Risk Assessments. This would provide clarity on what an IBC review of an HGT trial would include and would prompt the study team to think in terms of safety or identify safety related information. A revised Appendix M should include specific instruction to local IBCs to develop a collaborative process with their IRB of record to ensure input and oversight from both the IBC and IRB perspectives on SAE reporting and informed consent.

Current State of the NIH Guidelines and Expectations for IBCs

The notice indicates that “In particular, NIH seeks comment on whether the expectations of IBCs, in light of these proposed changes, have been articulated clearly in the proposed revisions to the NIH Guidelines.” We believe that they have not. The removal of Appendix M in its entirety leaves the expectations of IBCs unclear in a number of areas as indicated above. Further, the responsibilities and expectations for IBCs have been evolving beyond NIH Guidelines compliance. Timely information has not been forthcoming in addressing or supporting the role of IBCs vis-à-vis emerging technologies that are and reasonably can be predicted to impact HGT research. For example, registration of research utilizing CRISPR has not been provided an appropriate section within the NIH Guidelines. The NIH Guidelines are showing their age and need significant updating to substantively redefine and support evolving roles for IBCs. These efforts have been pursued at the local level and in many cases have managed to maintain the “spirit of the Guidelines” but are of necessity evolving away from the Guidelines as currently written. If this is the intent, then it must be clearly articulated in the Guidelines.

Recommendations:

- We recommend a comprehensive review of the NIH Guidelines to appropriately address relevant newly emerged and emerging technologies.
- We also recommend that NIH/OSP establish a task force to include scientists with the appropriate expertise (e.g., expertise in synthetic biology) from the regulated community to take this on.

The Role of the Recombinant DNA Advisory Committee (RAC)

We support purposed modifications to the RAC’s charter to “use the RAC as a public forum to advise on issues” and change the committee’s focus from research solely involving recombinant or synthetic nucleic acids to include research involving emerging technologies such as synthetic biology, CRISPR/cas9, gene drive, and other areas. However, that there is no entity at the NIH and specifically the OSP that is tasked with a role similar to that currently carried out by the RAC. If the intent is to defer this role to IBCs and empower additional oversight at the local level, then the intent must be clearly stated.

In absence of official RAC review, and given that the proposed changes to section IV-C-3 (pg. 41090) of the Federal Register notice indicates that “OSP shall serve as a focal point for information on recombinant or synthetic nucleic acid molecule activities and provide advice to all within and outside NIH...”, we ask that OSP identify a point of contact in the office who can serve as a resource for key questions, advice and guidance. OSP should ensure that it is able to provide expertise and guidance in response to inquiries from across the broad range of biomedical, pre-clinical, and clinical HGT research. In addition, there should be some mechanism through which to share findings during IBC review among multisite trials. Previously OSP performed this role, but under the new Guidelines if a site identifies a novel risk to a trial, other sites

could remain unaware of this risk. Perhaps the new Guidelines could include some language requiring dissemination/sharing of IBC site reviews. For instance, an IBC should be able to request a list of sites to which the protocol has been submitted and request the reviews and approvals (or disapprovals) of those sites.

Recommendations:

- Create a formal pathway to obtain feedback and guidance from OSP on all inquiries regarding recombinant or synthetic nucleic acid molecule activities.
- Consider a mechanism such as a web portal for information sharing during IBC review among sites engaged in multisite trials.

We appreciate the opportunity to comment on the proposed changes to the NIH Guidelines and remain available to provide additional information or discuss our recommendations.

Sincerely,



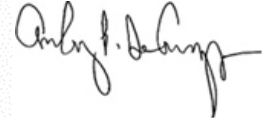
Ross McKinney, MD
Chief Scientific Officer, AAMC



Mary Sue Coleman
President, AAU



Peter McPherson
President, APLU



Anthony DeCrappeo
President, COGR

The Association of American Medical Colleges (AAMC) is dedicated to transforming health care through innovative medical education, cutting-edge patient care, and groundbreaking medical research. Its members comprise all 151 accredited U.S. and 17 accredited Canadian medical schools; nearly 400 major teaching hospitals and health systems; and more than 80 academic societies. The Association of American Universities (AAU) is an association of 60 U.S. and two Canadian preeminent research universities organized to develop and implement effective national and institutional policies supporting research and scholarship, graduate and undergraduate education, and public service in research universities. The Association of Public and Land-grant Universities (APLU) is a research, policy, and advocacy organization with a membership of 235 public research universities, land-grant institutions, state university systems, and affiliated organizations in the U.S., Canada, and Mexico, that is dedicated to strengthening and advancing the work of public universities. The Council on Governmental Relations (COGR) is an association of over 190 research universities and affiliated academic medical centers and research institutes. COGR concerns itself with the impact of federal regulations, policies, and practices on the performance of research conducted at its member institutions.