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Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, Maryland 20892-7985

RE: Proposed Action Under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (*NIH Guidelines*), Document number 2015-26388, 80 CFR 62543

Dear Director,

The American Biological Safety Association (ABSA International) welcomes the opportunity to comment on the *Proposed Action Under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*, Document number 2015-26388, 80 CFR 62543. ABSA International provides a critical expertise for this review as its members are extensively involved in implementing the *NIH Guidelines* and fulfilling certain roles specified therein.

The proposed outcome to streamline the review and approval process for human gene transfer research is an appreciated potential benefit to institutions that conduct extensive human gene therapy and human clinical trials and which possess a well-developed scientific expertise on their Institutional Biosafety Committee (IBC). The scientific expertise and human gene therapy review experience varies among IBC and Institutional Review Board (IRB) oversight entities. There is concern that the proposed actions allow for a much greater biosafety risk involving clinical human gene transfer experiments than the current process. More balance is needed between local and federal review of human gene therapy protocols than proposed in order to prevent mishaps involving human gene transfer research.

The following comments regarding the proposed action address: (A) concern that the fundamental changes in the role of the Recombinant Advisory Committee (RAC) vs. IBC review may *not* contribute positively to biosafety, especially at this time of technological breakthrough enabled by CRISPR/Cas9 and similar emerging technologies; and (B) the language of the proposed amendments must be altered for clarity so that institutions would be able to comply with the amended *NIH Guidelines* without ambiguity and confusion.

A. **Concern for the Restricted Scope of RAC Review Embodied in Proposed Amendments**

There exists a great diversity in the level of scientific expertise among IBCs, especially for the review of experiments that fall under *NIH Guidelines* Appendix M. Local IRBs and IBCs may not have the collective expertise to determine which proposed human gene transfer experiments are truly novel. Local IBCs or IRBs would be required to have high level knowledge of human gene therapy experiments previously reviewed by the RAC and the capacity to identify acceptable preclinical models if they will be expected to recognize when a protocol uses a new vector, genetic material, or delivery methodology, that represents a first-in-human experience or is based on preclinical safety data obtained using a new preclinical model system of unknown or unconfirmed value.

There is also great variety in the number and scientific breadth of reviews performed by IBC and IRB oversight bodies. The review of experimental uses of recombinant or synthetic nucleic acid molecules has always been an imperfect process that rests for the most part on the expertise of the local review committees – the IBC and other review committees. Will detailed training be required of all IBC members whose IBCs review submissions under appendix M to ensure consistent and adequate scientific review? Will the NIH require documented proof that the local IBC and IRB have the level of knowledge required to recognize when to request RAC review? Will NIH provide training and resources to IBCs, and approve/certify IBCs who demonstrate that they have the knowledge and experience to review clinical human gene transfer experiments?

Under the new guidelines, all human gene transfer protocols must be registered with the NIH, but they will no longer be reviewed by the RAC members. Instead, only those protocols for which local committees request an in-depth review will be examined. Many review committees may lack the resources or the ability to know when to request a RAC review under the newly proposed changes to the NIH Guidelines. Will the NIH registration process flag novel human gene therapy experiments that need RAC review based on the new proposed rules for which the IBC or Principal Investigator (PI) did not request RAC review? Many protocols may fall through the cracks.

The following <u>unintended consequences</u> are anticipated from the change of responsibility inherent in the proposed Amendments:

1. The Sponsor and the lead PI of a new study may no longer have assurance that their study will be reviewed by multiple world-class experts in their field. Many institutions have few or no IBC members whose technical recombinant / synthetic nucleic acid (rsNA) expertise is at the level of members of the RAC. The care with which some studies are designed and prepared might suffer from the knowledge that review may be less rigorous.

2. Local IBC's would make their review request determinations and the great majority of their final review decisions without the benefit of the RAC review. Their job will be more difficult and time consuming--and may be done less thoroughly--without the guidance from RAC.

3. Although the proposed amendments will lessen the RAC workload, they will greatly increase the workload for each local IBC because it must act on each study at least twice, in the knowledge that it is likely to be the sole guardian of biological safety for that study. The total person-hours devoted to biosafety review by local IBC members would be

expected to increase significantly because of the additional action and unshared responsibility for the review.

4. Investigators and possibly others at study sites will lobby local IBCs to recommend against RAC review because of the additional eight (8) weeks of review time that RAC review would entail. Under the current *NIH Guidelines*, the mandatory nature of RAC review compels that it be done early and removes the motive for such lobbying.

B. **Clarification of the Proposed Amendments.**

To implement the proposed amendments to the *NIH Guidelines*, a number of clarifying revisions are needed:

1. Participant Enrollment. Any institution that performs human gene transfer studies considers participant enrollment to be the most critical step that must be rigorously defined. The proposed amendments address the requirements for enrollment of study participants in seven separate passages, each including the phrase "No research participant shall be enrolled in a human gene transfer experiment until ..." (These passages are most easily found by searching on the word "enrolled.") All seven of these passages have different wording, and seem to establish somewhat different requirements for participant enrollment.
    1) The first passage requires only that the NIH registration process be completed.
    2) The second passage adds requirements for IBC and IRB approval and the NIH grant number.
    3) The third passage adds "all applicable regulatory organizations" but omits the grant number requirement.
    4) The fourth passage refers only to the IBC, but requires that final approval be issued only after the registration process is complete.
    5) The fifth passage restores the need for approval by other regulatory bodies, and adds that if RAC review is performed, the local IBC must consider both that review and the PI's response to the RAC before granting final approval. Critically, the fifth passage is the *only* one to require that the Appendix M reporting requirements be fulfilled.
    6) The sixth passage omits the safety reporting condition for IBC approval.
    7) The seventh and final passage requires only completion of the registration process, local IBC approval, and the NIH grant number.

    Ideally, the requirements for enrollment of study participants should be stated *only once* in the Guidelines, otherwise persons will compare all the statements and look for one that may be less rigorous. If the requirements must be stated more than once, their wording should include *all* requirements and be identical in every reference. The fifth passage stating the conditions for enrollment is the most comprehensive one in the proposed amendment, although it does not explicitly refer to the qualifications of the local IBC (passages 3 and 4) or to the NIH grant number (passages 2 and 7).

2. Clinical Trial Site Addition. We note that the second and seventh passages both refer to "a clinical trial site that is added after completion of the NIH protocol registration process." This text implies that registration is a one-time event for each study, so that sites added after registration need not register their own participation in the study. Is this intended? If so, OSP will not obtain a complete and current listing of all sites involved in a study. If, on the other hand, all trial sites including late sites *are* required to register, how will OSP respond to a late-joining site's request for RAC review of a study that did not have initial RAC review? Would this request be rejected peremptorily because the initial sites did not request review? Would the initial study sites have to re-approve after consideration of a RAC review successfully requested by a late-joining site?

3. Restated Requirements. The requirements for IRB approval, IRB-approved consent, the approval of "all applicable regulatory organizations", the NIH grant number, the adequacy of the IBC's composition, and the review of Appendix M information appear in some passages but not others. We believe that approvals from the IRB and "all applicable regulatory organizations" need not appear in the Amended Guidelines as they are already addressed by federal regulations. The adequacy of the IBC's composition and the requirement that it review Appendix M should be and are stated elsewhere in the *NIH Guidelines*, and these amended sections should not be burdened with the restatements.

4. IBC / IRB Coordination. While it is recognized that the proposed amendment allows for a RAC review to be requested for qualifying human gene transfer experiments (Section III-C-1), we believe that allowing the " ... NIH to make a determination, following a request from one or more *oversight bodies* [IBC and IRB] ... " to perform RAC review would lead to confusion and worsen what is already a recognized problem of coordination between the IBC and the IRB affecting human gene transfer research. What would be the NIH response to a case in which the IBC recommends RAC review, but the same site's IRB recommends no review? Even if the NIH considers the IBC's request for RAC review despite IRB's opposition, this dual request policy can only cause discord between the IRB and IBC. Each institution can direct its IBC to be sensitive to concerns of the IRB, but we believe it would erode the role and authority of the IBC if the *NIH Guidelines* invite the IRB to address the need for RAC review independently of the IBC.

The overarching concern for the proposed amendments to the *NIH Guidelines* is that the fundamental change of the review responsibility from the RAC to local IBCs may diminish the safety of rsNA research in the United States, especially if these amendments are implemented prematurely while the technology of rsNA is undergoing rapid and revolutionary change. The RAC or some other review body at the federal level that has the requisite broad expertise and knowledge in clinical human gene transfer studies and acceptable preclinical models should be engaged in the review process prior to approval of the study at the local level for all proposed studies. NIH should actively be involved in the review of all clinical human gene transfer studies whether or not they continue to the RAC.

The report "*Oversight and Review of Clinical Gene Transfer Protocols*" on which the proposed amendments are based, much of which was prepared in 2013, is now a dated analysis. In the last

year, the CRISPR/Cas9 technology has generated an explosion of non-clinical studies, sometimes involving multiple gene insertions, deletions, and/or fusions per cell. The greater complexity of genetic manipulation increases the difficulty of anticipating possible hazardous effects. CRISPR/Cas9 expands the accessibility of rsNA manipulations to a much wider spectrum of investigators because of its relative ease and modest cost. We believe that it would be prudent to maintain the primacy of the RAC embodied in the 2013 *NIH Guidelines*, at least until a representative group of human CRISPR/Cas9 studies has been initiated and their results followed for a reasonable period. Even one preventable death in human gene transfer can have a lasting impact on the field, and it would be tragic if such an event delayed development of the discipline at a time when its potential is so great.

Sincerely,

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President, American Biological Safety Association