Submission #2:

Name:	James Buchanan
Organization:	
Email:	james@planetintelligence.com
Comment:	While I am not a scientist, nor one who can claim clear understanding of the science involved in these processes, I do feel very strongly about any shortcuts taken in the name of corporate profits. I believe there are already far too many incorrect assumptions made and unleashed on what has become a 'guinea pig' population. The corporations involved have a free pass when it comes to liability so in my opinion, damn the profit, and err on the side of caution. Reinstate a safer review process.

Submission #3:

Name:	Philip Barruel
Organization:	University of California, Davis
Email:	prbarruel@ucdavis.edu
Comment:	I am generally in agreement with the changes proposed to the NIH Guidelines. One comment that I think should be modified is, "With the proposed elimination of the requirements for safety reporting under Appendix M, IBC oversight should be completed immediately after the last participant is administered the final dose of product." Specifically, the part about the IBC oversight being completed immediately after the last participant is administered the final dose of the product. I propose modifying this statement so that the IBC should assess how long a product may be shed by the participant and its oversight continue until either the product has been shown to no longer be shed by the study participant or it can be reasonably assumed to no longer be shed.

Submission #4:

Date	08/22/2018
Name:	Paul Gelsinger
Organization:	
Email:	(b)(6) - Personal Info.com
Comment:	As the father of Jesse Gelsinger, I am very concerned that the RAC's authority to review & approve or disapprove of IND's for gene transfer experimentation (what many call gene therapy) is being greatly diminished. Giving the FDA sole authority is a great mistake at this point. This technology has always showed promise, but has been massively over-hyped. I am aware that there have been a very few successes that can now be called therapy, but scientists do not yet understand all the complexities of interacting with the human genome. The first knowledge I had that things were wrong with the clinical trial that killed my son in September of 1999 was that the FDA had dropped the development of a Gene Therapy Information Network (GTIN). That network was being developed to disseminate adverse event data on gene transfer clinical trials to everyone conducting or planning to conduct clinical trials. The RAC knew the importance of this database & pressed the FDA representative in one of their quarterly meetings to explain why the effort was being discontinued. When I read in the RAC minutes the FDA reps candid remark that "my superiors answer to industry," I immediately was alarmed that the ethics of this technology was being compromised by the influence of money. The FDA failed my son in so many ways, and never accepted any responsibility for their failures when I confronted them. They pinned all the blame on the researchers, and yet they had the data in hand that should have stopped the clinical trial at one-tenth the dose of viral vector that my son received. So, if you believe that the system has fixed the financial conflicts of interest issues in clinical research, especially the over-hyped gene technologies, think again. Little has been done to place firewalls between the money and the research. The swinging door between the FDA and industry remains wide open. Our Congress can address this, but does not have the will. I haven't even touched on the reckless ambition of the University of Pennsylvania researcher who put Jesse in so much danger. He stood to gain enormously, both financially & career-wise, should the OTC trial have succeeded. But it didn't. His reckless disregard for the stop signs within the protocol directly led to my son's death. At the time of Jesse's death the role of the RAC had been subordinated to what they want to do again; they were not getting the information on the ongoing OTC clinical trial. That second level of oversight may have saved Jesse's life. We'll never know; they didn't have the opportunity. Please review the NOOH letter submitted to Dr. James Wilson 2+ years after Jesse's death. The FDA did its job but too late to help my son.

	https://www.fda.gov/regulatoryinformation/foi/electronicreadingroom/u Please do not let history repeat itself. The death of innocence is something that we all must carry, and is an almost overwhelming burden. Everybody failed Jesse Gelsinger, at every level, and all he wanted to do was help.

Submission #6

Name:	
Organization:	
Email:	
Comment:	Need to clearly line define (e.g., a checklist) what Institutional Biosafety Committees should review, what documents the IBCs should collect and how to report if there are any serious adverse events. The IBC depends on the NIH receiving and having careful review of all these studies and now it seems that is being taken away and now the Institution will have additional burden for oversight.

Submission #7

Name:	Evan Anderson
Organization:	Emory University School of Medicine
Email:	evanderson@emory.edu
Comment:	It would greatly help institutional biosafety committees if systematic guidance could be provided for CAR-T studies. These protocols increasingly fill Biosafety Committee meetings time and efforts (and are likely to further increase) despite there being minimal risk to study participants and study staff of risk of infection (with the nonreplicating viral vectors used to insert genes into autologous cells). If guidance could be provided that if CAR-T studies meet certain criteria, a standard approach could be used without need for full Biosafety Committee review, this would be greatly appreciated.

Submission #8

Name:	David W. Emery, PhD
Organization:	Independent Consultant, Clinical Gene Therapy
Email:	(b)(6) - Personal Info @gmail.com
Comment:	Please see attached file.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	- -

To: NIH Office of Science Policy
From: David W. Emery, PhD
RE: Comments on proposed amendments to the *NIH Guidelines*
Federal Registry Docket No. 2018–17785
Date: September 20, 2018

I am writing to provide comments on the proposed amendments to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*), Federal Registry Docket No. 2018–17785. I am providing these comments based on my experience of over 30 years as a researcher in the field of gene therapy, and on my experience of over 20 years as a biosafety professional. Regarding my expertise as a biosafety professional, I have served as the chair of Institutional Biosafety Committees for over 300 institutions conducting gene therapy clinical trials. In this capacity I have performed in-depth biosafety and clinical risk assessments for over 100 human gene transfer clinical protocols and chaired over 500 convened Institutional Biosafety Committee meetings to review gene therapy clinical trials.

In general, I support the proposed amendments to the *NIH Guidelines*. Specifically, I concur that the field of gene therapy has advanced to the degree that the NIH Recombinant DNA Advisory Committee (RAC) need no longer play a role in the safety assessment of clinical gene therapy studies, and that this role can instead reside with the Food and Drug Administration (DOI: 10.1056/NEJMp1810628) and local Institutional Biosafety Committees. However, I have several comments regarding the specifics of these amendments.

I have the following specific Comments:

Comment 1. The SUPPLEMENTARY INFORMATION section of the Federal Registry announcement indicates that: "With the proposed elimination of the requirements for safety reporting under Appendix M, IBC oversight should be completed immediately after the last participant is administered the final dose of product." However, the actual proposed amendments to the *NIH Guidelines* fail to mention this expectation. Further, I believe such an expectation would be inconsistent with the roles and responsibilities of IBCs and would ignore the post-dosing risks associated with some recombinant vectors. Specifically, I believe this expectation ignores the role of IBCs in considering the risk of vector shedding in the post-dosing setting. It is common practice for IBCs to continue oversight of research with animals when shedding of recombinant or synthetic nucleic acid molecule vectors is of concern, and I believe the same standard should be applied to the clinical gene therapy setting. I believe my concern can be addressed by revising the proposed amended language of Section IV-B-2-b-(1), which already indicates that "This review shall include: ...(iii) for recombinant or synthetic nucleic acid molecule research involving human research participants, assessment focused on biosafety issues (e.g., administration, shedding)." I propose that the following sentence be added at the end of this section: "Although IBC oversight is generally expected to conclude after the last participant is administered the final dose of product, individual IBCs may consider continuing oversight to account for vector shedding."

Comment 2. The SUPPLEMENTARY INFORMATION section of the Federal Registry announcement indicates that: "For instance, ClinicalTrials.gov has been instituted, which provides a transparent and searchable database for clinical trials." Although not specifically stated in the Federal Registry announcement, it appears that the proposed elimination of Appendix M clinical trial reporting requirements will result in the termination of GeMCRIS as a tool for tracking human gene transfer clinical trial data. Unfortunately, ClinicalTrials.gov is not currently formatted to serve as a "transparent and searchable database for clinical trials" involving human gene transfer. Specifically, ClinicalTrials.gov fails to include mandatory information fields that allow an individual clinical trial to be identified as involving human gene transfer (*NIH Guideline* terminology) or human gene therapy (FDA terminology) as was the case for information available through GeMCRIS. ClinicalTrials.gov also fails to include mandatory information fields regarding the genetic content and vector type used in trials that involve human gene transfer/human gene therapy. This missing information is exactly the type of information on which local IBCs rely when conducting risk assessments for human gene transfer clinical trials. If the NIH is

proposing to eliminate GeMCRIS as a database of human gene transfer clinical trials designed in part to assist local IBCs in their risk assessment of such trials, then it will be essential that ClinicalTrials.gov be revised to add specific mandatory fields that allow for the transparent identification of clinical trials that involve human gene transfer/human gene therapy, as well as the genetic content and vector type used in those trials. Without this information, ClinicalTrials.gov will be of no use to IBCs charged with assessing the biosafety risk of human gene transfer clinical trials at the local level.

Comment 3. Section III-C-1 of the amended *NIH Guidelines* states in part that "An individual patient expanded access IND is not research subject to the *NIH Guidelines* and thus does not need to be submitted to an IBC, if the following conditions are met..." I do not believe this is an appropriate carve-out from a biosafety perspective, in that the biohazard risks are no different for an expanded access human gene therapy IND than a conventional human gene therapy IND. This includes the biosafety risk to the clinical staff and to the general public.

Comment 4. Section I-E-4 is proposed to be amended to define the term "initiation" as follows: ""Initiation" of research is the introduction of recombinant or synthetic nucleic acid molecules into organisms, cells, or viruses." It is a surprisingly common misunderstanding on the part of researchers and sponsors engaged in human gene transfer research that the administration of cells containing recombinant or synthetic nucleic acid molecules to humans also constitutes human gene transfer. For this reason, I recommend that the definition of "Initiation" be revised to read as follows: ""Initiation" of research is the introduction of recombinant or synthetic nucleic acid molecules into viruses, cells, or organisms, including the introduction of cells containing recombinant or synthetic nucleic acid molecules into organisms."

Comment 5. Section IV-B-2-b-(1) of the amended *NIH Guidelines* states in part that "This review shall include: ...(iii) for recombinant or synthetic nucleic acid molecule research involving human research participants, assessment focused on biosafety issues (e.g., administration, shedding)". The two examples provided (administration and shedding) are far from an exhaustive list of biosafety issues that IBCs need to consider for human gene transfer clinical trials. IBCs also need to consider the items listed in subsections (i) and (ii) of this section when considering human gene transfer clinical trials. This issue could be addressed by revising subsection (iii) to read: "for recombinant or synthetic nucleic acid molecule research involving human research participants, assessment focused on the considerations stated above, as well as trial-specific biosafety issues (e.g., pharmacy activities, administration, shedding)." See Comment 1 above regarding other language I recommend for this section.

Comment 6. Section IV-B-7 of the amended *NIH Guidelines* states: "On behalf of the institution, the Principal Investigator is responsible for full compliance with the *NIH Guidelines* in the conduct of recombinant or synthetic nucleic acid molecule research." Because of the removal of most language regarding human gene transfer from the amended *NIH Guidelines*, I recommend that this sentence be revised to read: "On behalf of the institution, the Principal Investigator is responsible for full compliance with the *NIH Guidelines* in the conduct of recombinant or synthetic nucleic acid molecule research, including human gene transfer research."

Submission #7

Name: **Organization:**	James Trout, PhD
Email:	(b)(6) - Personal Info.net
Comment:	Eliminating the Recombinant DNA Advisory Committee (RAC) from performing a transparent and scientific review of Human Gene Transfer (HGT) clinical trials is of great concern and deemed inadvisable. Removing the RAC, a body of world-class experts, from being an integrated and defined component of NIH research oversight for recently emerged and emerging technologies has a negative impact on the safe conduct of research. The RAC is a body with technical expertise of a scale and breadth rarely accessible to research entities. While gene therapy, gene transfer, and gene editing technologies have moved from being an emerging technology to emerged in their biotechnology and clinical applications, as specified by the NIH Director and FDA Commissioner, the move to clinical research is recent. The emergence of CRISPR and CAR-T technologies opened the door to a wide variety of clinical applications yet we are still learning more about these technologies and their associated risks. The collective expertise on the RAC was invaluable in the review of novel, complex technologies and would continue to be so in this role, as well as in the continued review of recently emerged technologies. The exercise of RAC member responsibilities itself functions to continuously raise the level of expertise of its members and enables a holistic assessment for the multiple components participating in, or potentially affected by, research. Transparency in the process for soliciting RAC input, by inclusion in the NIH Guidelines, will continue to promote research rigor in study design and safety for all persons involved. The description for the RAC to exist as an advisory body in this subsequent proposed amendment to the NIH Guidelines is not sufficiently specific to be informative. It is unclear what the agenda will be for the RAC once it is removed from the NIH Guidelines. The plan for removal of the RAC, and for decisions previously made by the RAC to rest with the NIH Director and the Office of Science Policy (OSP), are of great concern particularly with regard to Major Actions (Section III-A-1). Decisions for research involving risk at the level of a Major Action should require expertise and input from the RAC, in a manner transparent to the public and in a procedure consistently applied. Concerns for the changing role of the RAC regarding adequate review and research oversight persist from the those raised in comment to 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, submitted by ABSA International on November 30, 2015, for what became the April 2016 Amendment. Changes to diminish the role of the RAC made in the 2016 NIH Guidelines amendment were substantial, significant, and unfortunately sufficiently recent to preclude an evaluation of the effect of those changes. There is no formal mechanism remaining in the amendment for the IBC to seek guidance from the RAC on specific

	concerns that arise during the review process. Previously, the referral of protocols for public RAC reviews served this purpose for the numerous institutions whose research calls for registered IBCs. The absence of the RAC's involvement in clinical research oversight is already being observed, restricting access to pertinent expertise not widely available, prior to completion of public review and official implementation of the proposed amendment. Many IBCs, excluding the long-standing academic medical centers traditionally at the forefront of gene therapy, lack the expertise to adequately conduct a risk assessment for clinical research as applied in pharmacy and clinical settings; and conversely, risk assessments and research oversight in clinics and hospitals differ vastly from the application of the NIH Guidelines and biosafety principles seen in the conduct of relevant pre-clinical research. According to the NIH Office of Science Policy (OSP, 26 August 2018), the last 10 years has seen a 59% increase in IBC registrations, which illustrates the rapid growth of this exciting clinical application. The majority of these IBCs are for locations which review HGT clinical research. For many locations, pharmacy and clinical staff have little to no experience in biosafety/biosurety and view the handling of HGT products akin to chemotherapy. The safe conduct of HGT trials requires appropriate risk assessments and significant education, particularly pertaining to the replication competent biologicals being utilized. Research test articles and technologies applied to human subjects retain the risks specific to the material involved, and potential risks are increasingly being reported (e.g., CAR-T cytokine release syndrome, additional CRISPR off-target effects, and significant genomic damage following CRISPR-Cas9 nucleic acid break repair). Considering recent evidence that CRISPR can impact DNA location megabases distant form the target site, expert review and oversight seems more critical than ever. The expertise of the RAC is clearly needed to provide far-reaching support for the safe research of

Submission #8

Name:	
Organization:	Immune Deficiency Foundation
Email:	lalbizo@primaryimmune.org
Comment:	On behalf of all people who are impacted by primary immunodeficiency diseases (PI), the Immune Deficiency Foundation (IDF) appreciates the opportunity to submit comments on the proposed changes to the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. We are excited by recent advancements in gene therapy, and in particular the potential gene therapy can offer to the PI community. The 2016 approval in Europe of Strimvelis to treat adenosine deaminase (ADA)-deficient severe combined immunodeficiency (SCID) and the ongoing clinical trials for gene therapy to treat X-linked SCID (X-SCID) are just two examples of these potential advancements in therapies. It is our great hope that these promising initiatives will continue and that sometime soon we will have gene therapy trials approved by the Food and Drug Administration (FDA) to treat PI. Background on Primary Immunodeficiency Diseases Primary Immunodeficiency diseases (PI) are a group of more than 350 rare, chronic genetic disorders in which part of the body's immune system is missing or functions improperly. Because of their condition, individuals with PI are far more susceptible to infections from even relatively modest viruses. A common treatment for many forms of PI is immunoglobulin (Ig) replacement therapy, which is derived from human plasma collected at plasma donation centers that undergoes a rigorous purification process before being developed into treatments. Regular, lifelong Ig treatments replace the antibodies the body is unable to produce, but it does not stimulate the patient's own immune system to make more Ig. The therapy can reduce the susceptibility to infections, optimize patient health, and improve their quality of life. Ig replacement therapy, however, is insufficient for those impacted by the most serious forms of PI, such as SCID. SCID occurs when there is combined absence of T cell and B cell function. There are at least 13 different genetic defects that can cause SCID, and these defects lead to extreme susceptibility to very serious infections. The severity of SCID means that infants who are not detected early often die without treatment via a hematopoietic stem cell transplantation (HSCT), or bone marrow transplant. Fortunately, the combination of such treatments and a nearly nationwide effort to screen newborns at

birth for SCID have led to far better outcomes than just a

With this progress in treatments, the PI community remains committed to additional advancements such as gene therapy for SCID and for the many forms of PI that lack such treatment options today. It is for these reasons that IDF has collaborated with developers of gene therapy treatments to offer individuals to serve on patient advisory boards and patient interview sessions. In addition, IDF is working with the Primary Immune Deficiency Treatment Consortium (PIDTC) to collect data gathered on patients with PI that will be used to examine treatment for SCID with HSCT and gene therapy. Further, IDF regularly shares updated gene therapy information at educational meetings and conferences as well as incorporating gene therapy material in IDF resources available online and in

IDF applauds the NIH for your proposal to streamline oversight of human gene transfer clinical research protocols and to reduce duplicative reporting requirements already captured within the existing regulatory framework. As the NIH and FDA noted in issuing this proposal, while such intense and overlapping oversight had its place, much has changed in recent years to justify a change that reduces regulatory burdens while still ensuring research participants are protected. We are supportive of streamlining this process as the gene therapy field has advanced to a state where such overlapping requirements are no longer needed and where the requirements no longer provide any enhanced protections to patients. We are also very enthusiastic about the prospects of gene editing as it relates to PI, and thus we are supportive of the redirection of resources to evaluating novel and emerging technologies such as gene editing. Particularly with finite resources, it is essential that all stakeholders ensure energies are expended where they are

Regarding specifics of the proposal, we think ceasing review of individual clinical gene therapy protocols by the NIH Recombinant DNA Advisory Committee is most appropriate. While the RAC served a very legitimate purpose in the initial gene therapy review process, it has now become redundant as the FDA’s role and expertise in clinical trials regulations has

We would propose, however, that the RAC continue to maintain the registry of U.S. protocols to allow for a public listing of all gene therapy trials. As you know, the RAC has maintained a registry for all clinical gene therapy protocols conducted in the

	U.S. through its Genetic Modification Clinical Research Information System (GeMCRIS) database. We are concerned that ceasing to operate this registry within the NIH would lead to this very important public resource becoming dated and no longer relevant. We have a strong preference for this registry because it contains more information that is specific to gene therapy than the clinicaltrials.gov website. As such, we urge you to revise the final rule to develop a proposal to maintain the registry either through the RAC or through another appropriate NIH or FDA database that will be kept up-to-date and provide a user-friendly searchable database of all gene therapy trials registered in the U.S. Conclusion IDF is grateful for the opportunity to comment on this important matter and hopes the NIH will give serious consideration to our registry suggestion. We look forward to working with the NIH regarding any changes to these guidelines and would welcome any questions you may have. If you have any questions, please contact Lynn H. Albizo, Senior Director of Public Policy, at lalbizo@primaryimmune.org.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/IDF-NIH-Gene-Therapy-Proposal-Comments-Oct 2018-FINAL.pdf

October 10, 2018

The Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, Maryland 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)

On behalf of all people who are impacted by primary immunodeficiency diseases (PI), the Immune Deficiency Foundation (IDF) appreciates the opportunity to submit comments on the proposed changes to the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. We are excited by recent advancements in gene therapy, and in particular the potential gene therapy can offer to the PI community. The 2016 approval in Europe of Strimvelis to treat adenosine deaminase (ADA)-deficient severe combined immunodeficiency (SCID) and the ongoing clinical trials for gene therapy to treat X-linked SCID (X-SCID) are just two examples of these potential advancements in therapies. It is our great hope that these promising initiatives will continue and that sometime soon we will have gene therapy trials approved by the Food and Drug Administration (FDA) to treat PI.

Background on Primary Immunodeficiency Diseases

Primary Immunodeficiency diseases (PI) are a group of more than 350 rare, chronic genetic disorders in which part of the body's immune system is missing or functions improperly. Because of their condition, individuals with PI are far more susceptible to infections from even relatively modest viruses. A common treatment for many forms of PI is immunoglobulin (Ig) replacement therapy, which is derived from human plasma collected at plasma donation centers that undergoes a rigorous purification process before being developed into treatments. Regular, lifelong Ig treatments replace the antibodies the body is unable to produce, but it does not stimulate the patient's own immune system to make more Ig. The therapy can reduce the susceptibility to infections, optimize patient health, and improve their quality of life. Ig replacement therapy, however, is insufficient for those impacted by the most serious forms of PI, such as SCID. SCID occurs when there is combined absence of T cell and B cell function. There are at least 13 different genetic defects that can cause SCID, and these defects lead to extreme susceptibility to very serious infections. The severity of SCID means that infants who are not detected early often die without treatment via a hematopoietic stem cell transplantation (HSCT), or bone marrow transplant. Fortunately, the combination of such treatments and a nearly nationwide effort to screen newborns at birth for SCID have led to far better outcomes than just a generation ago.

With this progress in treatments, the PI community remains committed to additional advancements such as gene therapy for SCID and for the many forms of PI that lack such treatment options today. It is for these reasons that IDF has collaborated with developers of gene therapy treatments to offer individuals to serve on patient advisory boards and patient interview sessions. In addition, IDF is working with the Primary Immune Deficiency Treatment Consortium (PIDTC) to collect data gathered on patients with PI that will be used to examine treatment for SCID with HSCT and gene therapy. Further, IDF regularly shares updated gene therapy information at educational meetings and conferences as well as incorporating gene therapy material in IDF resources available online and in print, including within the IDF Patient & Family Handbook.

Proposed Changes to NIH Guidelines

IDF applauds the NIH for your proposal to streamline oversight of human gene transfer clinical research protocols and to reduce duplicative reporting requirements already captured within the existing regulatory framework. As the NIH and FDA noted in issuing this proposal, while such intense and overlapping oversight had its place, much has changed in recent years to justify a change that reduces regulatory burdens while still ensuring research participants are protected. We are supportive of streamlining this process as the gene therapy field has advanced to a state where such overlapping requirements are no longer needed and where the requirements no longer provide any enhanced protections to patients. We are also very enthusiastic about the prospects of gene editing as it relates to PI, and thus we are supportive of the redirection of resources to evaluating novel and emerging technologies such as gene editing. Particularly with finite resources, it is essential that all stakeholders ensure energies are expended where they are needed most.

Regarding specifics of the proposal, we think ceasing review of individual clinical gene therapy protocols by the NIH Recombinant DNA Advisory Committee is most appropriate. While the RAC served a very legitimate purpose in the initial gene therapy review process, it has now become redundant as the FDA's role and expertise in clinical trials regulations has strengthened.

We would propose, however, that the RAC continue to maintain the registry of U.S. protocols to allow for a public listing of all gene therapy trials. As you know, the RAC has maintained a registry for all clinical gene therapy protocols conducted in the U.S. through its Genetic Modification Clinical Research Information System (GeMCRIS) database. We are concerned that ceasing to operate this registry within the NIH would lead to this very important public resource becoming dated and no longer relevant. We have a strong preference for this registry because it contains more information that is specific to gene therapy than the clinicaltrials.gov website. As such, we urge you to revise the final rule to develop a proposal to maintain the registry either through the RAC or through another appropriate NIH or FDA database that will be kept up-to-date and provide a user-friendly searchable database of all gene therapy trials registered in the U.S.

Conclusion

IDF is grateful for the opportunity to comment on this important matter and hopes the NIH will give serious consideration to our registry suggestion. We look forward to working with the NIH regarding any changes to these guidelines and would welcome any questions you may have. If you have any questions, please contact Lynn H. Albizo, Senior Director of Public Policy, at lalbizo@primaryimmune.org.

Sincerely,

John G. Boyle
President & CEO

Stem Cell Therapy and Gene Therapy

Chapter 25

Hematopoietic stem cell transplantation (HSCT) represents the mainstay of treatment for several severe forms of primary immunodeficiency diseases. Progress in cell manipulation, donor selection, the use of chemotherapeutic agents, and prevention and management of transplant-related complications has resulted in significant improvement in survival and quality of life after HSCT. In some forms of severe primary immunodeficiency diseases, gene therapy may represent a valid alternative for patients who lack acceptable stem cell donors.

Hematopoietic Stem Cell Transplantation

A "stem cell" is a type of cell that can divide over and over and produce more stem cells as well as descendant cells that turn into different types of cells Embryonic stem cells, for instance, can make descendants that turn into any tissue in the body, like skin cells, brain cells, heart cells etc For each organ in the mature body, there are specific stem cells that can make all the different kinds of cells in that organ For example, in the blood system, hematopoietic ("blood-forming") stem cells (HSC) give rise to each of the different types of blood cells such as red blood cells (RBC), white blood cells (WBC) and platelets

Traditionally, HSCs were obtained from the bone marrow This process was called "bone marrow transplantation " However, new methods now obtain HSC from peripheral blood, or blood taken from the placenta at birth ("cord blood") Cord blood, in particular, provides an excellent alternative source of HSC for the immune and blood systems The process of taking HSCs from one person and transfusing them into another is called hematopoietic stem cell transplantation, or HSCT Unlike transplantation of a solid organ (such as a kidney or liver), HSCT does not involve surgery It is more similar to a blood transfusion But instead of just blood, the fluid transfused contains HSCs

The primary immunodeficiency diseases for which HSCT is most commonly performed include Severe Combined Immune Deficiency (SCID), Wiskott-Aldrich Syndrome (WAS), IPEX Syndrome, Hemophagocytic Lymphohistiocytosis (HLH) and X-linked Lymphoproliferative Disease (XLP) It can also be used in the treatment of Chronic Granulomatous Disease (CGD) and many other severe primary immunodeficiency diseases The transplantation of HSCs from a "normal" individual to an individual with a primary immunodeficiency disease has the potential to replace the deficient immune system of the patient with a normal immune system and, thereby, affect a cure

There are two potential obstacles that must be overcome for HSCT to be successful The first obstacle is that the patient (known as the recipient or host) may have enough immune function remaining after the transplant to recognize the transplanted stem cells as something foreign The immune system is programmed to react against things perceived as foreign and tries to reject them This is called graft rejection In order to prevent rejection, most patients require chemotherapy and/or radiation therapy to weaken their own residual immune system enough to prevent it from rejecting the transplanted HSCs This is called "conditioning" before transplantation Many patients with SCID have so little

(Hematopoietic Stem Cell Transplantation continued)

immune function that they are incapable of rejecting a graft and do not require conditioning before HSCT

A similar situation occurs when the recipient's bone marrow is full of its own, defective stem cells and the HSC cannot find anyplace to establish themselves This is called "failure of engraftment " To prevent this, chemotherapy may be given to reduce the number of defective HSC in the recipient's bone marrow in order to "make room" for the new HSC to engraft

Although the chemotherapy treatment prevents the host from rejecting the transplanted HSCs, it may cause serious side effects These include transient loss of all of the cells of the bone marrow so the patient is very susceptible infections, anemia (low RBC) and bleeding problems due to low platelets Chemotherapy also may cause severe blistering of the mouth or other mucous membranes that makes getting adequate hydration and nutrition very difficult It is because of these serious complications that HSCT is reserved for those patients with the most severe immune defects

The second obstacle that must be overcome for the transplant to be successful is Graft versus Host Disease (GVHD) This occurs when the mature T-cells from the donor or which develop after the transplant, perceive the host's tissues as foreign and attack these tissues To prevent GVHD, medications to suppress inflammation and T-cell activation are used These medications may include steroids, cyclosporine and other drugs

In order to prevent some of these potential obstacles, it is important to try to identify a "matched" donor A matched donor is one whose Human Leukocyte Antigens (HLA) are the same as those of the recipient

Selecting a Donor

HLA are tissue types Each of us has our own collection of HLA antigens on our cells including the cells of our immune system and bone marrow, as well as on cells in most other tissues and organs The exact structure of these HLA antigens is determined by a series of genes clustered on the sixth (6th) human chromosome Compatibility of HLA is very important to determine the chance of successful engraftment while keeping the risk of GVHD low

There are many different variants for each of these HLA genes in humans The combination of HLA alleles of each individual is relatively unique However, since the HLA genes are closely clustered on chromosome 6, they are usually inherited as a single unit Therefore, the chance that an individual's brother or sister shares the same HLA alleles is relatively high

There is a 1 in 4 chance that any sibling could be a perfect match for the patient Unfortunately, due to the laws of probability and the fact that most families have a limited number of children, fewer than 25% of patients have a sibling who is a "match " Therefore, there has been a major effort to develop alternative methods to offer the possibility of a transplant to patients who do not have a matched donor in their own family

One alternative is to try to find a suitable matched donor through one of the worldwide computer-based registries of individuals who have volunteered to serve as bone marrow donors The National Marrow Donor Program in the U S has listings of hundreds of thousands of individuals who have provided a blood sample to have their HLA type measured Similar registries are present in many countries around the world

(Selecting a Donor continued)

Information on the combination of HLA alleles of more than 19 million volunteer donors is collected in Bone Marrow Donors Worldwide (BMDW) This database can be easily accessed by authorized healthcare professionals to explore the possibility that there is a matched unrelated donor (MUD) available for a patient who needs HSCT and does not have an HLA-matched donor in the family

Successful transplants for patients with a primary immunodeficiency disease using donors found through this worldwide registry have saved the lives of many patients over the past 20 years Results of transplantation using fully matched unrelated donors for some diseases now approaches the success rate for transplants using sibling matches

Another source of HSC used for transplantation in patients with primary immunodeficiency diseases is umbilical cord blood In the growing fetus, HSC frequently leave the marrow and are found circulating in high numbers in the blood At the time of birth, the placenta can be recovered, the blood that is remaining removed and the HSC isolated and banked These cord blood HSC may then be HLA typed and used for transplantation Since cord blood contains fewer mature T-lymphocytes than the marrow or blood of adult donors, sometimes cord blood transplants have been successful even though the degree of match between donor and patient was not very good One limitation of cord blood HSC transplantation is that because of the limited volume of umbilical cord blood, there may not be a sufficient numbers of HSC to treat a larger child or adult

If a perfect match cannot be identified, it is sometimes possible to use one of the parents as a donor Either parent has half of the same alleles as the patient; the parent is said to be "haploidentical" to the patient There are some problems that can occur with this type of transplant The mature T-lymphocytes contained in the bone marrow of the haploidentical parent would be able to recognize the HLA alleles that are unique to the patient, and would thus cause GVHD

In order to prevent this complication, it is essential to remove the mature T-lymphocytes (called T-cell depletion) from the bone marrow before infusing the stem cells into the patient This is done with a preparative regimen before the transplant After the mature T-cells are removed from the HSC, the risk of GVHD is markedly reduced

T-lymphocytes of donor origin that develop from the transplanted HSC and reconstitute the patient's T-lymphocyte immunity will remain haploidentical to the rest of the cells of the patient However, the risk of GVHD from these T-lymphocytes is low because these cells develop inside the new host from immature precursor cells in the grafted marrow Like a person's own T-cells, they are "educated" during their maturation to ignore or "tolerate" the cells and tissues of the host

It may take as long as six to eight months for the stem cells to reconstitute T-lymphocytes and for these newly generated T-cells to mature and learn to work with other cells in the host Therefore, restoration of immune function after T-cell depleted HSCT takes longer than after fully matched HSCT (where mature T-lymphocytes contained in the graft may immediately provide some immune function)

Sometimes, complete immunologic reconstitution may not occur after HSCT In some cases after haploidentical T-cell depleted HSCT, more than one transplant has to be performed to achieve T-cell reconstitution Full immune reconstitution (including antibody production) is achieved less often than after fully matched transplantation

Some centers use T-cell depleted HSCT for treatment of babies with SCID who do not have a matched family donor, while other centers believe that the search for a

(Selecting a Donor continued)

matched unrelated donor is the best first choice option The best choice depends on many factors including:

- The type of SCID or primary immunodeficiency disease
- How much immune function remains
- The degree of matching of potential donors
- The types of HSCT available (cord blood vs bone marrow)
- The age of the patient
- How sick they are and what types of complications they have had

Procedures

HSC are "harvested" from the donor by removing bone marrow from the pelvic bones Bone marrow is removed by drawing the marrow up through a needle that is about 1/8 of an inch in diameter Only two teaspoons are taken from each puncture site because, if more is taken, the sample is diluted with the blood that flows through the bone marrow space Bringing blood with the bone marrow increases the risk of the sample carrying the mature T-cells that have the potential to cause GVHD

Usually, two teaspoons are taken for each two pounds of the recipient's body weight The average donor might have only a few punctures performed to get enough stem cells for a baby, but more than 100 punctures may be required to get enough stem cells for a teen or full sized adult The procedure may be performed under general anesthesia or under spinal anesthesia The discomfort after the procedure varies from donor to donor

Almost all donors will require some type of pain control medication for two to three days after the procedure, but most donors are not required to stay in the hospital overnight and are able to return to full activity shortly afterwards The donor's immune system is not compromised because HSC and marrow quickly regenerate

Once it has been harvested, the bone marrow is passed through a fine sieve to remove any small particles of bone and processed further, if necessary, to remove incompatible red blood cells, or to remove T-cells It is then placed into a sterile plastic bag and infused into the host intravenously just like a blood transfusion

As an alternative to bone marrow harvesting, HSC can be obtained from peripheral blood and then purified via a process known as apheresis The donor's blood is collected from an arm vein, using a needle that is connected with a machine that removes the white blood cells After white blood cells are removed from the blood, the remaining red blood cells are then returned to the donor via a vein in the opposite arm The HSC are then purified from the other white blood cells Typically, in order to enrich the amount of HSC in peripheral blood, the donor receives subcutaneous injections of granulocyte-colony stimulating factor (G-CSF) or of plerixafor in the days that precede the blood collection Both G-CSF and plerixafor mobilize the HSC from the bone marrow, transferring them into peripheral blood, so that a large number of HSC are present in the peripheral blood before the apheresis procedure

Results of HSCT

HSCT between HLA matched siblings has been successfully employed in the treatment of primary immunodeficiency diseases since 1968 The first child to receive a transplant (a patient with X-SCID) is still alive, healthy and has a family of his own This case suggests that, as best as can be determined, the graft is very long lasting and appears to be permanent

In the case of infants with SCID, HSCT involving a matched marrow has minimal graft versus host disease risk and is associated with an overall success rate of as high as 90% Results of HSCT from unrelated donors from a haploidentical parent are not as good, yet approximately 60-80% of the infants survive and demonstrate robust T-cell reconstitution

The chance of survival depends on the health of the patient at the time of the transplant If the patient is in relatively good health, free from infection at the time of the transplantation and does not have lung damage from previous infections, the outlook is very good Because of this, survival is very good (>90%) in infants with SCID who receive HSCT within 3-4 months of age, even when the donor is not a family match This emphasizes the importance of early recognition of SCID, and the benefit of newborn screening for this disease, that is BEFORE the patient has a serious infection

While reconstitution of the number and function of T-lymphocytes is the rule after HSCT for SCID, normalization of antibody production occurs in some, but not all, patients Reconstitution of antibody production after HSCT for SCID depends on the specific form of SCID, on the type of donor (matched vs haploidentical) and on the use of chemotherapy as part of the preparative regimen before the HSCT If antibody production is not reconstituted after HSCT, patients will require Ig replacement therapy indefinitely to help protect them from infection Even if replacement therapy is required, these patients usually enjoy a good quality of life after transplant

HSCT is also an effective form of treatment for other forms of primary immunodeficiency diseases, including WAS, IPEX, HLH), XLP, X-linked hyper-IgM (also known as CD40 ligand deficiency), CGD and other primary immunodeficiency diseases

In most of these conditions, conditioning with chemotherapy is required before the transplant to allow engraftment of donor-derived stem cells, even when the donor is a matched sibling The success rate after HSCT from an unrelated donor in these cases is nearly as good (70-80% survival) as using a matched sibling for the donor Here again, the initial health of the patient is extremely important and the best survival rates are in children who are transplanted under the age of 5, who are relatively free of infections and who do not have pre-existing lung or liver damage

Mixed chimerism (that is persistence of the patient's immune cells along with donor-derived white blood cells) after HSCT is sufficient to cure the disease in many of these disorders (IPEX, HLH, XLP, X-linked hyper-IgM, CGD), and this may allow doctors to use less intense chemotherapy, thus also reducing the risk of related toxicity In boys with WAS, mixed chimerism is associated with a higher risk of complications (autoimmunity, persistence of low platelets) and more intense chemotherapy regimens are typically used for this disease

HSCT is not always indicated in patients with CD40 ligand deficiency and CGD, as many of these patients do well on medical management The risks and benefits of the procedure must always be carefully weighed

It must be noted that HSCT from a haploidentical parent is not as successful in primary immunodeficiency diseases other than SCID and is typically reserved to very severe cases that cannot be safely managed otherwise Again the risks and benefits must be carefully addressed

Gene Therapy

Most primary immunodeficiency diseases are caused by errors (mutations) in specific genes It has long been the hope that one day it would be possible to cure these diseases by fixing the mutation that causes the disease and thus affect a cure As a result of the human genome project and similar efforts to map all of the genes present in human beings, we now know the identities of the specific genes involved in many diseases, including the vast majority of primary immunodeficiency diseases More genes are being identified nearly every week We have finally reached the stage where that long held hope is becoming a reality

Not every genetic disorder, including some primary immunodeficiency diseases, will eventually be correctable by gene therapy However primary immunodeficiency diseases, as a general rule, may be better suited for this therapy than almost any other class of genetic disease Transplantation of HSC taken from a normal donor has been successful in curing many of these disorders, so it should theoretically also be possible to take the patient's own HSC and correct the genetic defect in those cells by adding a normal copy of the gene that is causing the disease

To introduce the gene, we take advantage of the ability of some viruses (retroviruses) to penetrate into cells and to insert their genome into the patient's own DNA For the purpose of gene therapy, viruses have been modified so that their own genes have been largely removed and replaced with the normal copy of the defective human gene that is causing the primary immunodeficiency diseases

To perform gene therapy, the patient's HSCs are first isolated from the bone marrow or from peripheral blood, and they are then cultured in the laboratory with the virus containing the gene of interest Various growth factors are added to the culture to make HSC proliferate and to facilitate infection with the virus After two to four days, the cultured cells are washed to remove any free virus, and then they are transfused into the patient The cells that have incorporated the gene of interest into their chromosomes will pass it to all cells that will be generated when these cells divide Because the gene has been inserted into HSC, the normal copy of the gene will be passed to all blood cell types, but not to other cells of the body Because primary immunodeficiency diseases are caused by gene defects that affect blood cells, this can be sufficient to cure the disease

Gene therapy represents a life-saving alternative for those patients with severe forms of primary immunodeficiency diseases, who do not have a matched sibling donor In these cases, performing an HSCT from a haploidentical parent or even from a MUD would carry some significant risks of GVHD In contrast, GVHD is not a problem after gene therapy, because in this case the normal copy of the gene is inserted into the patient's own HSC, negating the need for a HSC donor

Until now, gene therapy has been used to treat patients with SCID secondary to adenosine deaminase (ADA) deficiency, X-linked SCID, CGD and WAS The first clinical trial of gene therapy was at the National Institutes of Health in 1990 and treated a 4-year-old girl with ADA deficiency The design of this first trial did not attempt to correct the defective HSC, only the T-cells This girl is now clinically well and still has about 25% of her circulating T-cells carrying the corrected ADA gene more than 20 years after her treatment After this initial clinical trial demonstrated that gene therapy could be carried out safely and that gene-corrected T-cells could survive for years and function normally, follow up trials were initiated attempting to cure children with ADA-SCID by targeting HSC for gene correction The results have been spectacular with most of the more than two dozen ADA-SCID patients attaining a significant long lasting increase of the T- and B-lymphocyte count

(Gene Therapy continued)

and a remarkable improvement of immune function Importantly, no episodes of serious adverse reactions or cases of leukemia have occurred in the patients with ADA deficiency treated by gene therapy

The next primary immunodeficiency disease to be treated by gene therapy was X-linked SCID This trial also targeted the HSC using a retrovirus to deliver the gene Beginning with a groundbreaking study in Paris followed by a similar experience in London, there have been 20 X-SCID babies around the world that have been treated with gene therapy In these infants, gene therapy was performed without any need for chemotherapy prior to the transfusion of HSC that had been cultured with the virus Eighteen of these patients are currently alive, and in 17 of these 18 children gene therapy alone was sufficient to restore development of T-lymphocytes and immune function and no other treatment was needed

Unfortunately, while the SCID was cured, five of these patients developed leukemia Four of the children's leukemia was cured, but one child died

Gene therapy trials are ongoing with patients with other primary immunodeficiency diseases Overall, the experience with gene therapy in primary immunodeficiency diseases has demonstrated that it is possible to cure the disease by inserting a normal copy of the gene into the patient's HSC However, there are some risks that need to be overcome and safer vectors need to be developed Various laboratories around the world are working at modifications of the viral vectors in order to improve their safety Nevertheless, gene therapy must still be regarded as an experimental therapy It is likely that the inherent problems will be worked out in the coming years and that a larger number of primary immunodeficiency diseases will be cured by gene therapy

Gene Therapy: What You Should Know

Many primary immunodefciency diseases (PI) are caused by errors, or mutations, in specifc genes. It's because of this that there has been the hope that it would be possible to fx the mutation that causes the disease, essentially curing it. The Human Genome Project, which was the international, collaborative research program whose goal was the complete mapping and understanding of all the genes of human beings, and similar efforts have allowed researchers to identify specifc genes involved in many types of PI.

There are more genes being identifed regularly. While not every genetic disorder will be able to be corrected by gene therapy, it's still important for members of the PI community to understand their options when it comes to treatment, including gene therapy.

What Is Gene Therapy?

In short, gene therapy is a technique that uses genes to treat or prevent disease. In the future, this technique may allow doctors to treat a disorder by inserting a gene into a patient's cells instead of using drugs or surgery. Gene therapy only works for conditions where a single gene is the cause. Researchers are testing several approaches to gene therapy, including:

- Replacing a mutated gene that causes disease with a healthy copy of the gene
- Inactivating, or "knocking out," a mutated gene that is functioning improperly
- Introducing a new gene into the body to help fght a disease

Challenges of Gene Therapy

While gene therapy is a promising option for some conditions, it is still being researched and developed through ongoing trials. Currently, there are FDA approved gene therapy treatments, but there are not yet any for PI.

Overall, the experience with gene therapy in PI has demonstrated that it is possible to cure the disease by inserting a normal copy of the gene into the patient. There are some risks, however, that need to be overcome and the safety needs to be improved. As of now, gene therapy must be regarded as an experimental therapy that is being researched through on-going clinical trials with individuals with PI, of which there are quite a few.

To learn more about gene therapy and to fnd out more about the process, please visit: www.primaryimmune.org/gene-therapy.

DID YOU KNOW?

The frst clinical trial of gene therapy was at the National Institutes of Health in 1990 and treated Ashanthi DeSilva, a 4 year old girl with ADA SCID, a type of Severe Combined Immune Defciency (SCID) with mutations in a gene that encodes an enzyme called adenosine deaminase (ADA).

Michael Blaese, MD with Ashanthi DeSilva (left) and Cindy Kisik, who was also born with ADA-SCID and treated with gene therapy, at the IDF 2013 National Conference, June 29.

Cindy and Ashanthi in 1992 with the pioneer physicians of gene therapy: (from left) French Anderson, MD; Michael Blaese, MD; and Kenneth Culver, MD.

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If you haven't created your account yet, sign-up today! If you already have an account make sure you're logging in to select your preferences, update your information or check out what's new. www.primaryimmune.org/my-account.

Submission #9

Date	10/10/2018
Name:	Lisa Nichols
Organization:	COGR
Email:	lnichols@cogr.edu
Comment (limit: 15,000 characters):	Attached are joint comments from the Council on Governmental Relations (COGR), Association of American Medical Colleges (AAMC), Association of American Universities (AAU), and Association of Public and Land-grant Universities (APLU) on Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. We appreciate the opportunity to comment on the proposed changes and remain available to provide additional information or discuss our recommendations.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/Final Joint Association Comments on Proposed Changes to the NIH Guidelines.pdf

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

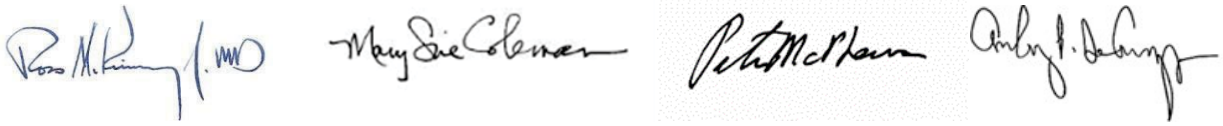
could remain unaware of this risk. Perhaps the new Guidelines could include some language requiring dissemination/sharing of IBC site reviews. For instance, an IBC should be able to request a list of sites to which the protocol has been submitted and request the reviews and approvals (or disapprovals) 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	Mary Sue Coleman	Peter McPherson	Anthony DeCrappeo
Chief Scientific Officer, AAMC	President, AAU	President, APLU	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.

Submission #10

Name:	
Email:	
Comment:	The administration of last rites to the RAC as represented by the proposal to amend the NIH Guidelines is unfortunate but inevitable. As NIH moves toward stripping the RAC of the last vestiges of its bully-pulpit authority, please consider the following concerns of a former RAC member: (1) The NIH Director and the RAC membership almost certainly have different perspectives about what protocols stand in need of public review and discussion. Thus, noting that the Director has sent only 3 protocols to the RAC since removing the RAC's own decisionmaking authority in 2016 hardly counts as proof that it is no longer needed. (2) Similarly, it is quite clear that FDA and the RAC have different perspectives on both the science and the ethics of gene transfer research. The difference between what the RAC approved and what the FDA later changed without notice to the RAC almost certainly played a key role in Jesse Gelsinger's death. Moreover, the FDA's ability to address research ethics questions has by no means improved since that time – not out of unwillingness as much as lack of time, person power, and resources. This situation will not be ameliorated by eliminating RAC review. (3) Transparency is essential to safe research, and RAC and FDA have always stood in opposition regarding the public availability of clinical trial data. Protection of trade secrets and confidential commercial information in clinical trials is by definition detrimental to the interests not only of research subjects in those trials but also of patients seeking treatment in the future. The reason is simple: no industry actor engaged in research wants competitors to know what research pathways it is taking, or to allow competitors to learn from its mistakes. This makes trials longer, dead-end research more common, and avoidable injury to research subjects more likely. Eliminating RAC review (along with GemCRIS and the GTSAB) does avoid duplication, but at the cost of losing even the modest amount of transparency that RAC has been able to preserve. (4) IBCs and IRBs still need guidance when reviewing gene transfer research protocols. Simply ditching Appendix M might not be the best way to proceed. If there is a way to preserve its guidance in some separate form that is available to them should

	they wish to consult it, that would be a worthy effort for OSP to (5) Finally, and most important, the RAC's public role has been vital in educating the public about gene transfer research. NIH has made an exciting promise to modify the RAC charter in order to reconstitute it as a standing public forum able to advise the NIH Director about the scientific, ethical, legal, social, and policy implications of a broader range of emerging biotechnologies, such as gene editing and gene drives, some regenerative medicine technologies, some synthetic biology (such as SHEEFs), and other developments as yet unimagined. The rapidity with which the biosciences are moving novel interventions onto the clinical translation pathway requires responsive, anticipatory, and extensive public engagement and thoughtful discussion. Thus, NIH's promise absolutely must be kept – yet at present it is merely a vague assertion. I cannot recommend strongly enough that this RAC reinvention is essential to public discussion, public education, and comprehensive consideration of the implications of novel biotechnologies. Please revise the charter and engage the
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/King-2002-The_Journal_of_Law,_Medicine_&_Ethics copy.pdf

RAC Oversight of Gene Transfer Research: A Model Worth Extending?

Nancy M. P. King

Clinical gene transfer research (GTR) has both a unique history and a complex and layered system of research oversight, featuring a unique review body, the Recombinant DNA Advisory Committee (RAC).[1] This paper briefly describes the process of decision-making about clinical GTR, considers whether the questions, problems, and issues raised in clinical GTR are unique, and concludes by examining whether the RAC's oversight is a useful model that should be reproduced for other similar areas of clinical research.[2]

CLINICAL GENE TRANSFER REsEARCH OVERSIGHT

Clinical GTR is governed by the same oversight system as most clinical trials, with a significant addition: the RAC. Like other research with human subjects, GTR, if it is affiliated with a federally funded institution, must be approved by an institutional review board (IRB) whose activities are governed by the common rule, that is, the federal regulations for protection of human subjects in research.[3] Like other research intended to produce a drug, device, or biologic to be marketed in the United States, GTR is alsooverseen by the Food and Drug Administration (FDA).[4] Institutions conducting GTR may also subject it to additional local oversight.5

The unique additional oversight applies to all GTR taking place at institutions receiving federal funding for recombinant DNA (rDNA) research. Receipt of any federal funding for rDNA research brings to bear the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules.[6] Before the advent of clinical GTR, this meant that the funded institution needed to establish an institutional biosafety committee (IBC) to address issues of biosafety and containment in the production, use, and transport of genetically engineered organisms. The local IBC reviewed proposed activities that fell within the scope of the NIH guidelines under the guidance of the RAC. The RAC was established as a federal advisory committee in 1974 and held its first public meeting in February of 1975, immediately after the Asilomar conference on rDNA research.7 From 1975 until the early 1980s, the RAC set the safety standards for all recombinant DNA research being conducted in the United States. These standards became the NIH guidelines.[8]

The RAC recognized early that the future of GTR was in humans. Before the first human study was even contemplated, it began to consider the issues that would be raised by human research protocols using gene transfer interventions. Aworking group on human gene therapy was established in 1984 as a subcommittee to the RAC, and began developing guidelines for human GTR. Those guidelines, known as the Points to Consider,9 were completed in 1985, several years before review and approval of the first gene marking study. It was not until 1990 that the first trial of a potentially therapeutic gene transfer intervention began; the first subject was a 4-year-old girl.[10]

The history of the RAC is interesting, complicated, and well-described elsewhere.[11] Its functions have changed over rime. Since the RAC undertook review of clinical GTR, all clinical GTR protocols connected with an institution receiving any federal rDNA funding must be submitted to the Office of Biotechnology Activities (OBA)[12] for RAC review and potentially for public discussion. Since not all GTR takes place at institutions doing federally funded rDNA research, some GTR (especially that taking place outside of the United States) is not required to be reviewed by the RAC. At the urging of the FDA (which reviews any research anywhere

*Journalofl.Aw,Medicine&Ethics,*30 (2002): 381-389.

that is intended to produce products to be marketed in the United States), however, many such studies are voluntarily submitted to OBA by the sponsor. The additional layer of federal oversight, linked to funding, that is specific to this field of research provides a unique opportunity to examine its progress. Whether GTR merits or needs this scrutiny is and has been a subject of considerable debate.[13]

I became a member of the RAC in September 1998, after it had been reengineered several times but before the death of Jesse Gelsinger in September 1999 engendered new scrutiny.[14] As an experienced nonscientist IRB member, I found it challenging to understand the RAC's role. For review of individual protocols, RAC most closely resembles a combination of central IRB[15] and scientific study section. In addition, it has unique public and policymaking functions, which predate its role in protocol review.

According to Dr. LeRoy Walters, who served on the RAC for many years, crafting and understanding the RAC's protocol review role has been a challenge since that role was initiated. In his testimony before the Senate subcommittee conducting hearings on GTR oversight after the death of Jesse Gelsinger, Dr. Walters explained that in the mid-1980s, the RAC worked toward reviewing individual GTR protocols in part because no other entity was prepared to do so. **He** noted that:

> gene-therapy research was clearly a hybrid field. On the one hand, it was highly technical and required the expertise of molecular biologists and human geneticists. On the other hand, gene-therapy research was human-subjects research, which was governed by its own set of rules and which was quite comprehensible to laypeople.[16]

Dr. Walters considers RAC review of GTR, as detailed in the Points to Consider, to reduce to four "rather simple and straightforward" questions:

- What are the potential harms and benefits of the research to the research subjects who will participate in a planned study?
- How will these potential harms and benefits be communicated to prospective research subjects, so that they can make voluntary and informed decisions about whether to participate in the research?
- How will the selection among potential research subjects be made in **a fair** and equitable **way,** especially in cases where more people want to participate than can be enrolled in a study?
- How will the privacy of research subjects be protected and the confidentiality of their medical information preserved?[17]

It is clear that all these questions apply to many other areas of clinical research in addition to GTR. Thus, it has always been, and continues to be, reasonable to ask whether GTR merits - or benefits from - this additional oversight.

Is GENE TRANSFER RBEARCH UNIQUE?

Clinical GTR is generally referred to, in both professional and popular contexts, as "gene therapy." This terminology persists despite extensive - and to some extent successful - efforts to replace it, in scientific and policy documents and consent forms, with "gene transfer research." Clinical gene transfer trials only began in 1990, and the vast majority of trials have been early-phase studies (only 1 percent being Phase III trials),[18] so it is not and should not be surprising that effective treatments have not yet emerged. Nor should it be surprising that, in a complex and technically challenging field that encompasses not only a vast range of diseases and a wide variety of genetic interventions, but also an extraordinary diversity of vectors and routes of administration, definitive promise has only been hinted at in several distinct areas of research.[19] Yet public and professional enthusiasm for the irresistible logic of the concept of gene therapy, and enormously concentrated media attention on this both fascinating and potentially frightening field, have resulted in what might legitimately be termed "irrational exuberance"[20] about the prospects for the field as a whole and the outcome for individual subjects enrolled in gene transfer trials.

Is GTR different enough from other early-phase clinical research to warrant its unique system of oversight? The first step in addressing that question is to consider those characteristics that produce decision-makingchallenges. One is the field's complexity: gene transfer is a methodology that is used not only for correction of single-gene defects, but also for insertion of genes for other purposes, most notably, to stimulate the immune system (as in anticancer vaccine and immunotherapy studies), to render cancer cells susceptible to antiviral medications, and to stimulate the growth of collateral blood vessels to circumvent blocked arteries in the limbs or in the heart. The technical challenges here are staggeringly multifarious, as is the variety of means of introducing new genetic material. Importantly, the means of achieving dosing consistency across studies is, like the field itself, largely in its beginning stages.[21]

A second characteristic of GTR is the lack of good animal models of disease. This is not, of course, a problem unique to gene transfer, but it may be concentrated here. Certainly there are more mouse models than there are models in larger animals or nonhuman primates, but as a RAC colleague once commented to me, "Everything works in mice." Until Jesse Gelsinger died in September 1999, gene transfer was widely viewed as extremely safe in comparison with other research and treatment modalities, so that moving from preclinical to clinical trials, while necessarily

invoking many unknowns, did not appear to pose much danger to human subjects.[22] Yet even before Mr. Gelsinger died, it was recognized that, as is the case for many biologics, dose-dependent safety and efficacy of gene transfer interventions is difficult to predict. Unlike the most common pattern associated with drug research, a reasonably steady rise in both beneficial and harmful effects with increasing doses, many gene transfer interventions show an elbow graph associated with a threshold effect; that is, nothing happens until a threshold dose is reached.[23] In an early trial, then, there may be few clues as to when anything is going to happen, and it can be extremely difficult to anticipate what will happen, good or bad, at the threshold point.

These characteristics produce a great deal of uncertainty in this field - perhaps more uncertainty than in most other clinical research. In addition, some of the unknowns loom especially large, as they include the possibility of permanent changes in subjects, and even inadvertent germ-line transmission of changes to subjects' offspring. Any such changes could be positive, negative, both, or neither. These uncertainties in particular give gene transfer its high public profile, for both good and ill. To borrow some terminology from science fiction writer Neal Stephenson, GTR is both "mediagenic" and "mediapathic,"[24] because the public has a long history of being both fascinated by and fearful about its potential.[25]

Several shifts in emphasis and concern in clinical GTR over its short history have compounded these challenges. First, as I have already noted, the birth of the field was associated with expectations about potential cures for monogenic diseases. Cystic fibrosis, sickle cell disease, the hemophilias, and a variety of other serious disorders affecting relatively small numbers of persons were the earliest areas of research interest. At present, however, the vast majority of gene transfer studies (about 70 percent) are oncology studies.[26] Oncology research is a very large field, with its own culture, its own model consent forms, its own federal institute complete with clinical trials weblist, and a powerful commitment to clinical research.27 The shift in emphasis from monogenic disease to cancer has a variety of potential implications. It makes GTR more like other early-phase clinical research, much of which is also cancer research; thus, what happens in GTR may have broader implications for all clinical research. Yet a shift away from seeking cures for rare and largely untreatable disorders could ultimately have broad financial and social justice effects as well.[28]

A second shift relates to perceptions about the most salient risks in GTR. At the outset, insertional mutagenesis and inadvertent germ-line transmission were of great concern. Mr. Gelsinger's death engendered a shift of concern to vector toxicity and helped to spur the ongoing effort to develop safer gene delivery methods, both viral and nonviral. Currently, both vector toxicity and germ-line transmission are areas of heightened concern.[29] The challenge is to determine the magnitude and likelihood of these disparate risks of harm and their appropriate limits. As clinical gene transfer gets closer to demonstrating efficacy, the even greater challenge is to determine whether - and if so, how - to balance the potential for efficacy against the risk of germ-line effects. Germ-line effects pose risks not to subjects but to their offspring. If any germ-line effects materialize at all, they are highly likely to be harmful; however, in theory, they could result in persistent correction of the defect.

Finally, the shift that has garnered the widest attention since September 1999 is the shift in funding sources for clinical GTR, from NIH and the large pharmaceutical companies to small venture biotechnology companies, often investigator-founded in partnership with academia. The problem of financial conflict of interest and the policy question of financial disclosure and what to do with the information (prohibit conflicts, manage conflicts, disclose them to potential subjects and/or to the IRB) long predated Mr. Gelsinger's death, but the revival of interest in conflict of interest management and reporting that directly resulted therefrom extends to all federally funded research and beyond.Jo

THE BFNCH TO BEDSIDE BALANCE

Taken together, the implications of GTR's salient characteristics may be seen as either inherently or only temporarily needing the increased scrutiny that the field has enjoyed. There have been many arguments made over the years by industry, investigators, potential subjects, and at times the FDA, that the RAC is unnecessary, duplicative, burdensome, and an obstacle to research progress.JI Yet it is undeniable that RAC review provides a public window onto the entirety of an unprecedented and exciting field. From my perspective as a RAC member, this window illuminates, through public meetings and publicly available information, important questions about research design and ethics that are not clearly or systematically showcased in any other forum: when is the right time to move to humans, and who should be the first subjects? Since these are questions that must be answered during the development of any line of research, what marks them as of special interest in GTR? It is simply that, for GTR, these questions are asked by the RAC.J[2]

Why does it matter that the RAC asks these questions? There are two reasons. First, the other oversight entities that might also ask have different relationships to the questions and may be inconsistent or incompletely attentive in their approaches. The FDA asks them, but not publicly. Local IRBs may or may not ask them, as local IRBs differ in their capacity and willingness to interrogate the scientific merit of research proposals.JJ The RAC, with its resources and combination of expertises, is the sole entity perfectly positioned to ask these questions about GTR. In addition, because GTR is still highly concentrated on early-phase trials, these questions come up over and over again for the RAC, as they do not in many other fields. Second, by virtue of its public

process, the RAC has the opportunity to foster responsible inquiry into these questions, throughout a broadly constituted field in which a range of different answers to the questions may be contemplated.

When to move from bench to bedside

Moving from preclinical research to research with human subjects requires making several key determinations: (1) that enough preclinical information has been gathered so that the only reasonable way to learn more is from human studies; (2) that the risks of harm have been minimized, the potential for gaining knowledge has been maximized, and the amount of uncertainty has been reduced as far as is feasible by the gathering of preclinical information; and (3) that the remaining risks and uncertainties are small enough that it is fair to ask human subjects to take part in the research. In GTR, the answers to these questions depend on a wide variety of study-specific characteristics, including the availability of animal models, the characteristics of the intervention under study, and the burden of the disease under study. A complex balancing process is required - one that is not only scientific but also inherently ethical and, ultimately, societal.[34] The balancing act depends on what is balanced, and what is balanced changes from study to study.[35] Thus, an entity like the RAC has the capacity, since it sees the whole field through many different studies, to articulate the components of the balancing calculation. A rigid formula is neither expected nor desirable, but other oversight bodies may be expected to enhance their examination of this question through attention to the RAC's example.

Who should be the first subjects?

Closely intertwined with the "when" question is the "who" question. In selecting the first human subjects for an experimental intervention, the first consideration should be how subject selection furthers the goals of research; that is, how subject selection minimizes risks and maximizes the contribution of the research to generalizable knowledge. For which subjects can harms be meaningfully minimized, and from which subjects can the best information be gained? It is possible that these two goals, both of which must be met in scientifically and ethically sound human subjects research, could be in conflict. Such conflicts present interesting challenges for study design, as the aftermath of Mr. Gelsinger's death made apparent.[36]

Generally speaking, there are two models for choosing the first subjects: the pharmacology model and the oncology model. As I have previously discussed,[37] the sickest-first (oncology) model and the healthiest-first (pharmacology) model have both been used in GTR. There are different reasons for using each, based on characteristics of the line of research and the disease under study. What is important is that the breadth of the field requires that both models be considered, whereas outside GTR it is not at all uncommon for the proponents of one model to use it exclusively and to consider the other inherently unethical. For example, some hospital-affiliated IRBs are astonished to hear that healthy volunteers are routinely enrolled in Phase I trials of pharmaceuticals, because they cannot benefit, yet are subjected to some risk. These same IRBs may be accustomed to thinking that sick subjects necessarily can benefit from Phase I trials simply because they have the disease of interest, a proposition about which IRBs less closely connected to medical centers are better positioned to be skeptical. Here again, the RAC's capacity to articulate the component factors of a determination about study population provides it with the opportunity to model this discussion throughout clinical GTR and even throughout all of clinical research.

THE OFFICE OF BIOTEOiNOLOGY ACTIVITIES AND THE RECOMBINANT **DNA** ADVISORY CoMMTITEE TooAY

The RAC's complicated recent history includes a brief and confusing hiatus: a reduction in size and a reconstitution of its mission from public review of all studies to selection of only those presenting new, important, or unsolved scientific, ethical, and social issues; and its recent, strengthened emergence from a challenge to its continued existence, with reexpanded membership and enhanced support staff and resources in OBA.[38] An important goal for OBA is increased education for investigators and local oversight bodies, IRBs in particular, about GTR and the RAC. At present, the legacy of past confusion still looms large, in part because even institutions whose IRBs review a lot of GTR have a relatively limited experience of GTR review in comparison with other fields, simply because the overall volume of GTR is small. Thus, what IRBs need to know about GTR presumably needs to be relearned periodically.

Recently, when forty-three IRB chairs and representatives were interviewed about their understanding of federal review of GTR,[39] ten of forty-three respondents burst into laughter at the question. Seventeen of the forty-three IRB respondents in this sample exhibited a detailed comprehensive understanding of the nature and process of RAC oversight; twenty more provided accurate but basic information. Furthermore, many of the IRB representatives interviewed emphasized their active role in seeking information from RAC, FDA, and other oversight bodies, and/or requiring the investigator to keep them fully informed, citing numerous information sources and mechanisms for information acquisition. Yet fourteen interviewees (including some of those who gave the most complete explanations of federal review) expressed their uncertainty, confusion, and desire to have a better understanding of federal oversight. In my experience, gained from conversations, discussions, and workshops with IRB members during my tenure on the RAC, as well as from

public comments at RAC meetings, some misconceptions persist. Many IRBs think RAC approves GIR-and thus that failure of RAC to select a study for full public review is an approval. Other IRBs see every word from every RAC member as embodying a mandate. These views are better replaced by understanding RAC as a substantive but advisory body with expertise that supplements IRBs' expertise, while the IRB has independent authority to approve or disapprove GTR.

Many IRBs want *OBNRAC* advice and guidance in conducting review (especially when they feel in need of additional scientific expertise), but some don't know if it is permissible to ask for help. Some IRBs are unaware of Appendix M, the Points to Consider, from the NIH guidelines. This ignorance cuts them off from an important source of information that they ought to consider, namely, the material prepared by the investigator for OBA in response to Appendices **M-11** through **M-V;** oreover, it can lead to clashes between M-III (informed consent) requirements and IRB consent form templates.[40] Finally, IRBs often want and need feedback from RAC, but don't always see - or follow up on - correspondence from OBA.[41]

For as long as I have been a member of the RAC, and especially in the aftermath of September 1999, OBA has been working to improve subject protections and information and communication about GTR for the research community and the public. Efforts are underway to dispel the above noted gaps and misconceptions. First, NIH has mandated changes that increase attention to (1) data-monitoring, (2) conflicts of interest (required by Appendix M-III since 1990 but not always addressed in RAC review before September 1999), and (3) research ethics education.[42] Second, in October 2000 the so-called timing action was instituted, which permits (but does not require) investigators to submit protocols to *OBNRAC* simultaneously with submission to the local IRB.[43] In the past, RAC review was required to follow local IRB approval; thus, RAC's oversight was unlikely to serve an educational function for the IRB or to aid in its deliberations about the protocol. Now that IRB review usually comes after RAC review, IRBs are better able to make use of RAC guidance.

Third, it is now easier for local IRBs to know how and where to find RAC guidance,[44] particularly from those protocols that are not publicly reviewed. Most protocols (70-80 percent) are *not* selected for full public review and discussion because they do not present novel or unresolved important scientific or ethical questions.[45] However, there is a significant resource for local IRBs to be found in the RAC's process of determining whether a protocol merits full public review. This process has matured considerably in the last several years. Each RAC member now reviews all submitted protocols, with Appendix M responses and consent forms, in order to vote on whether full public review is warranted. Voting is conducted by email, and OBA facilitates the circulation of questions and comments between and among RAC members, investigators, and sponsors. Importantly, this email correspondence is public. Even more importantly, it often serves to clarify issues that may be of concern to local IRBs. RAC members' questions (even though they are individual observations and not the product of committee consensus) may help focus the IRB's review, and the answers to those questions may help provide crucial additional information to the IRB, and even reassure them that the investigator has satisfactorily addressed the principal concerns. Recently, OBA amended its information letters to the investigator, which are copied to the principal investigator's IRB, to include information on how to request the electronic correspondence file for a protocol not selected for full public review and discussion. This was done largely for the benefit of IRBs.

A fourth key development that has finally been accomplished after much hard work by OBA is the so-called harmonization action. Even before Jesse Gelsinger's death, it was recognized that some sponsors resisted full reporting of adverse events to *OBNRAC,* out of concern that adverse events reports contained confidential commercial information that would necessarily be made public because they were sent to OBA. When Mr. Gelsinger died, the extent of the underreporting became clear,[46] and technical disparities between reporting requirements to *OBNRAC* and the FDA loomed as a stumbling block to increasing compliance (and the use of the reported information to inform the field and protect subjects). The harmonization action, recently finalized,[47] makes it possible for investigators to report the same adverse events to both the FDA and OBA simply by filing the same reports in two places at the same time.

Also addressed as part of the harmonization action are two critical issues that have been sources of concern to some investigators and industry representatives: the disclosure of confidential commercial information, and the risk of alarming the public by dumping raw unanalyzed adverse event information into the public domain. Both of these problems may be alleviated by the establishment of two new entities, the Gene Transfer Safety Advisory Board (GTSAB) and the Genetic Modification Clinical Research Information System (GeMCRIS).

The GTSAB is a kind of nontraditional super-data safety monitoring board. It will be composed of some RAC members, some FDA members, and *ad hoc* consultants as needed; it will review the data emerging from all GTR, in order to identify and compare trends across studies, and in order to place emerging data in context to enhance public and professional understanding. Reports from the GTSAB will be presented at RAC meetings.[48]

The GeMCRIS database has been under development by OBA for several years.[49] OBA has already made much information on GTR protocols available online and in electronic form.[50] The database, currently being beta-tested, will be searchable in a variety of ways and will have firewalls limiting

different visitors to different degrees of access - including access by the general public.

Since the RAC's reinvention in the mid-1990s, its capacity for and interest in activities with policy, educational, and cross-study implications has increased. Developments like the GTSAB and the GeMCRIS database represent the RAC's public and policy-directed functions, rather than its function of individual protocol review. They reflect both the use of scientific expertise and the goal of public information; they require collaboration and promote information sharing with other agencies and entities; and they offer important innovations. Data safety monitoring boards are most commonly created to review only one study; the cross-study capabilities of both GTSAB and GeMCRIS are precedent-setting. In addition, a newly constituted RAC Working Group on informed consent, established at the March 2002 meeting, is currently developing guidance on consent forms and the consent process in GTR. Because GTR has unique aspects but also shares many critical characteristics with other early-phase trials, this work is expected to have useful implications for other early-phase clinical research.

CONCLUSION: MODEL OR HURDLE?

The RAC is an accident of history that represents a historical opportunity to provide insight into important questions about early-phase, cutting edge clinical research. Some have argued that as the field matures, the RAC will outlive its usefulness.[51] If GTR is just like any other area of research, that might be true - but only if no questions remain to be asked.

GTR has been called a "canary in the mine,"[52] and in some respects it has proven to be the canary several times over: with respect to conflict of interest, adverse events reporting, media hype, and the therapeutic misconception. It has raised some issues, such as inadvertent germ-line effects and reproductive health issues, that could and should have been addressed by others long before now (in oncology research, for example). It has raised other issues, such as in utero research, that have bearing in other fields (in maternal-fetal surgery, for example). Finally, it has raised still other issues that will almost certainly arise in new areas of research yet to be developed (such as xenotransplantation and the production of transgenic organisms). Thus, even though the RAC model's applicability to new areas of controversial research has been questioned,[53] the RAC has proven itself able to successfully draw attention to questions that have broad applicability across clinical trials.

If RAC is a model, the characteristics that make RAC-like extra scrutiny necessary and valuable should be determined; historical accident is not sufficient. GTR garnered scrutiny because of public concern over the uncertainties, risks, and apparent promise of the field. Yet what RAC has to contribute arises not from these characteristics alone, but from its expertise and from the promise of producing generalizable guidance that can be of use to oversight bodies having local control. New and sexy issues in science catch public and professional attention and appear to be the most natural candidates for extra scrutiny; yet some of RAC's most important contributions are coming from its review of common questions and problems that have not been systematically addressed in less prominent areas of research.[54]

Thus, in my view, RAC is indeed a model, but determining where the RAC model is best duplicated is not an easy question. New RACs should not be established for each emerging mediagenic/mediapathic research field. Instead, the model should be extended when overarching umbrella review and field-wide guidance is needed and useful; cross-study analysis of research data for a field is both possible and desirable; and public access and education are desired. Careful review of the entire clinical research enterprise could suggest that, if judiciously located, more RACs are better than one.

ACKNOWLEIXiEMENTS

My colleagues on past and current ELSI projects have been instrumental in the development of my thinking, as have my colleagues on the RAC and in OBA; my views on GTR and the RAC are, however, entirely my own.

REFERENCES

1. The acronym also serves as a homonym for an instrument of medieval torture, a meaning that is wryly invoked both by investigators and sponsors who appear before it and by members after long meetings.

2. Others have also addressed the question whether the Recombinant DNA Advisory Committe (RAC) oversight model, or aspects of it, should be more broadly applied. See, e.g., L. Walters, "The Oversight of Gene Transfer Research," *Kennedy Institute of Ethics journal,* 10 (2000): 171-74;}. Rainsbury, "Biotechnology on the RAC - FDNNIH Regulation of Human Gene Therapy," *Food and Drug Law Journal,* 55 (2000): 575-600.

3. The consolidated and harmonized Common Rule was published at 56 Fed. Reg. 28,012 Uune 18, 1991); the codification most familiar to institutional review boards (IRBs) and others involved in research oversight are the Department of Health and Human Services regulations at 45 C.F.R. Part 46 (2001).

4. The Food and Drug Administration (FDA) regulations corresponding to the Common Rule appear at 21 C.F.R. Parts 50 and 56. Key FDA drug development regulations are also found at Parts 312, 314, and elsewhere. The FDA's human subjects regulations are substantially similar to the Common Rule, but in addition, the FDA has a very hands-on relationship with research sponsors in the long process of drug development. See, e.g., the overview provided in N. Plant, "Adequate Well-Controlled Clinical Trials: Reopening the Black Box," *Widener Law Symposium Journal,* 1 (1996): 267-97.

5. Clinical gene transfer research (GTR) may also be subject to additional local review in several forms. If it is cancer research (as most of it is), there may be a local oncology protocol review committee. If there is a general clinical research center affiliated

with the institution at which the research will take place, the general clinical research center's review committee must also review the research, if any part of it will take place in the general clinical research center. And some institutions have established their own human gene transfer review committees.

6. The National Institutes of Health's (NIH) guidelines are available on the Office of Biotechnology Activities website, *at* <http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html> (last visited September 17, 2002). They were first published in 1976, and have been amended many times.

7. At the Asilomar conference, molecular biologists lifted a voluntary 1974 moratorium on recombinant DNA research and set forth principles to guide its regulation. See, e.g., M. Rogers, *Biohazard* (New York: Knopf, 1977); P. Berg et al., "Asilomar Conference on Recombinant DNA Molecules," *Science,* 188 (1975): 991-94; J.P. Swazey et al., "Risks and Benefits, Rights and Responsibilities: A History of the Recombinant DNA Research Controversy," *Southern California Law Review* 51 (1978): 1019-67.

8. Statement of Dr. LeRoy Walters, Director, Kennedy Institute of Ethics, before the Senate Subcommittee on Public Health, Committee on Health, Education, Labor and Pensions, Feb. 2, 2000.

9. The Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Research Participants is Appendix M of the NIH guidelines *(supra* note 6). Appendix M was added to the NIH guidelines in 1990.

10. See, e.g., L. Walters andj.G. Palmer, *The Ethics of Human Gene Therapy* (New York: Oxford, 1997); Rainsbury, *supra* note 2; National Reference Center for Bioethics Literature, Scope Note 24, Human Gene Therapy, *at* http://www.georgetown.edu/research/nrcbl/scopenotes/sn24.html> (last updated March 2002).

11. See Walters and Palmer, *id.;* Rainsb11ry, *supra* note 2.

12. The Office of Biotechnology Activities (OBA) is the NIH office that staffs the RAC. It was formerly called the Office of Recombinant DNA Activities; in recent years it has been expanded and also staffs two other federal advisory committees, on xenotransplantation and genetic testing.

13. The history of this debate is detailed in the sources cited *supra* notes 8 and 10.

14. Rainsbury, *supra* note 2. Eighteen-year-old Jesse Gelsinger was the first subject to die as a direct result of gene transfer. See S.G. Stolberg, "The Biotech Death of Jesse Gelsinger," *New York Times Magazine,* Nov. 28, 1999, at 137-51.

15. That is, it functions something like a single IRB established to provide overarching guidance to local IRBs for a multicenter study. In this respect, RAC is a kind of precursor to the current interest in centralizing some aspects of the oversight of multicenter trials.

16. See Walters, *supra* note 8.

17. *Id.*

18. Statement of Dr. Amy Patterson, Executive Director, OBA, before the Senate Subcommittee on Public Health, Committee on Health, Education, Labor and Pensions, Feb. 2, 2000, *at* <http://www4.od.nih.gov/oba/rac/documents1.htm> (last visited September 17, 2002).

19. Promise has been shown to date in several hemophilia studies (see, e.g., J. Stephenson, "Gene Therapy Trials Show Clinical Efficacy," *Journal of the American Medical Association,* 283 (2000): 589-90); in recent studies of infants and young children with one form of severe combined immunodeficiency (S. Hacein-Bey-Abina et al., "Sustained Correction of X-Linked Severe Combined Immunodeficiency by ex Vivo Gene Therapy" N. *Engl.]. Med.,* 346 (2002): 1185-93); and in a few studies of squamous cell carcinoma of the head and neck (the only GTR that has as yet reached Phase III trials).

20. I have of course borrowed this phrase from Alan Greenspan, who used it in a very different context. The terms more commonly used to describe the degree of excitement about GTR are somewhat more pointed, like "hype". See, e.g., E. Marshall, "Less Hype, More Biology Needed for Gene Therapy," *Science,* 270 (1995): 1751-52. See also L.R. Churchill et al., "Genetic Research as Therapy: Implications of 'Gene Therapy' for Informed Consent," *Journal of Law, Medicine & Ethics,* 26, no. 1 (1998): 38-47.

21. In GTR, genes are introduced into subjects in a variety of ways. Each means of introduction needs a precise and consistent standard for measuring and reporting the amount of genetic material, in order to control dosing and quantify outcomes. Most GTR uses delivery vectors to introduce the genetic material, though some studies use naked DNA. Vectors can be made of altered viruses or of other materials, like fat particles. Each vector used in GTR therefore needs to be individually standardized. Because most vectors are viral, there are so many in use, and each is so different, this standardization is a considerable undertaking. See discussions of vector standardization guidelines for retroviruses and adenoviruses in RAC meeting minutes, December *2000,at* <http://www4.od.nih.gov/oba/RAC/meeting.html> (last visited September 17, 2002). The National Gene Vector Laboratories are instrumental in developing standards, *at* <www.ngvl.org> (last visited September 17, 2002).

22. The trial in which Mr. Gelsinger took part was the first human study to attempt to introduce a replacement for the defective gene in his enzyme deficiency disorder, ornithine transcarbamylase deficiency. This deficiency impairs the liver's ability to metabolize nitrogen, resulting in an excessive and damaging accumulation of ammonia. The protocol used a gene-delivery vector made from a genetically altered adenovirus to introduce the potentially corrective gene into the liver via the hepatic artery. As is characteristic of viruses, viral gene delivery vectors cause an inflammatory response, which apparently affected Mr. Gelsinger's liver and went on to have overwhelming systemic effects. See extensive discussion in the minutes of the December 1999 RAC meeting, *at* <http://www4.od.nih.gov/oba/RAC/meeting.html> (last visited September 17, 2002).

23. *Id.* at comments of Dr. Anne Pilaro, FDA, in RAC meeting minutes, December 1999.

24. N. Stephenson,*'Zodiac* (New York: Bantam Books, 1995).

25. Sources of concern range from the original Asilomar moratorium on recombinant DNA research to discussions of germ-line interventions, both deliberate and inadvertent. See, e.g., the many sources cited in the Human Gene Therapy Scope Note, *supra* note 10.

26. Possible explanations for this shift are structural, financial, scientific, and social. Cancer is a problem that affects many people and is high in public consciousness. The apparatus of oncology research is large, prominent, and experienced in attracting research funding and managing clinical trials. And burgeoning knowledge in areas relating to cancer control mechanisms, such as the role of the immune system and of various genetic mutations, has helped lead to many forms of GTR in cancer: gene-based vaccines, the introduction into tumors of genes that can be killed by antiviral agents, and studies using tumor suppressor genes are just a few examples. As of May 31, 2002, there were 332 cancer trials in OBA's database, out of 480 total clinical trials of interventions considered potentially therapeutic. This total excludes marking studies and studies using healthy normal subjects. If all human studies are included, the per-

centage of cancer studies is about 63 percent of the total; data *at* <http://www4.od.nih.gov/oba/rac/documents1.htm > (last visited September 17, 2002) (enumerated in the last two pages of the Protocol List).

27. The National Cancer Institute's informational website on oncology research is very comprehensive, *at* <http://www.cancer.gov/clinical_trials/> (last visited September 17, 2002). For some insight into the perspective of oncology research, see M. Miller, "Phase I Cancer Trials: A Collusion of Misunderstanding," *Hastings Center Report,* 30, no. 4 (2000): 34-43.

28. Focusing GTR on monogenic diseases could be viewed as a vital component of the ongoing effort to develop effective interventions for patients with orphan diseases. Moving GTR to more common diseases and disorders with multifactorial causes, like cancer, HIV infection, coronary artery disease, or diabetes clearly makes a promising technology more widely available. At the same time, however, it does two additional things: it greatly increases the investment of money and research infrastructure for GTR; and it helps to focus public and policymaking attention on research involving expensive, cutting-edge technologies as a primary solution for problems that can also be addressed by attention to prevention, public and environmental health and health education, lifestyle, and the complex relationships among genes, environment, and expression.

29. See, e.g., RAC meeting minutes, March 1999, December 2001, and March 2002 for discussions of inadvertent germ-line effects, *at* <http://www4.od.nib.gov/oba/RAC/meeting.html> (last visited September 17, 2002). See also RAC, NIH report, *Prenatal Gene Transfer: Scientific,Medical and Ethical Issues,* NIH Pub. No. 00-4720 (released in January 2000 following the January 1999 Gene Therapy Policy Conference on the topic),*available at* <http://www4.od.nih.gov/oba/RAC/meeting.html> at "January 7-8, 1999, Prenatal Gene Therapy: Scientific, Medical, and Ethical Issues-Full Report."

30. See, e.g., D. Shalala, "Protecting Research Subjects - What Must Be Done," *N. Engl.]. Med.,* 343 (2000): 808-10; National Institutes of Health, "Financial Conflicts of Interest and Research Objectivity: Issues for Investigators and Institutional Review Boards," #OD-00-040, June 2000, *at* <http://grants2. nih. gov/grants/guide/notice -files/N OT-O D-0 0-040.html> (last visited September 17, 2002); Office for Human Research Protections, "Draft Interim Guidance: Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider When Dealing With Issues of Financial Interests and Human Subject Protection," *at<http://* ohrp.osophs.dhhs.gov/humansubjects/finreltn/finmain.htm> (last visited September 17, 2002); M. Cho et al., "Policies on Faculty Conflicts oflnterest at U.S. Universities,"*JAMA,* 284 (2000): 2209-14; S.V. McCrary et al., "A National Survey of Policies on Disclosure of Conflicts of Interest in Biomedical Research," *N. Engl.]. Med.,* 343 (2000): 1621-25; K. Morin et al., "Managing Conflicts of Interest in the Conduct of Clinical Trials,"*JAMA,* 287 (2002): 78-84. Dr. James Wilson, then-director of the University of Pennsylvania's Institute for Human Gene Therapy, where the ornithine transcarbamylase deficiency trial took place, and a co-investigator, had a financial interest in a company he founded, Genovo Inc., which had a stake in the success of the trial's liver-directed gene transfer methodology, developed by his laboratory at Penn. See D. Nelson and R. Weiss, "Hasty Decisions in the Race to a Cure?," *Washington Post,* Sunday, Nov, 1999; at A0l, for a review of the potential financial conflicts of interest and how they were viewed before Mr. Gelsinger's death.

31. See *supra* notes 7 and 10.

32. See, e.g., Report of the RAC, **NIH,** *supra* note 29, especially speaker paper, J. Sugarman, "Ethical Questions Related to the Prospect of in utero Gene Transfer Experiments," at 71-75.

33. Other entities, such as oncology protocol review committees, general clinical research centers, institutional biosafety committees, local human gene transfer committees, and review committees convened by sponsors, may have scientific but not ethical expertise, or may not be disposed to ask certain scientific questions.

34. Indeed, the three determinations are nothing more than my own phase I-specific gloss on the federal Common Rule's first two criteria for IRB approval of research, codified in Department of Health and Human Services regulations at 45 CFR 46.11l(a), which addresses the IRB's overall responsibility to approve only research that minimizes risks and that demonstrates an appropriate balance between the risks of harm and the benefits from anticipated gains in knowledge.

35. For example, the nonexistence of a "knockout mouse" model, genetically altered to knock out a gene of interest and therefore mimic a particular human disorder, is not the same as the limitations of the information that can be gained from knockout mice about human disorders; nor is it the same as the knowledge that there is a knockout mouse available but that purchasing the right to use it from the patent holder is costly and will delay the start of a Phase I study in humans.

36. Choosing the right first subjects posed unexpected challenges in the ornithine transcarbamylase deficiency trial. At least three different possible subject populations were apparently discussed at various times: severely affected newborn infants currently in crisis from an excess of ammonia; severely affected but currently stable infants and young children awaiting liver transplant; and partially affected adults (usually men and women with a late onset fOfm of the enzyme deficiency; Mr. Gelsinger, who had been diagnosed at 3 years of age, apparently had a spontaneous mutation rather than an inherited form of the disorder). One important consideration in choosing subjects is the ethical preference for first recruiting adults who can make their own decisions about research participation. This consideration is especially powerful in first human trials because of the extreme uncertainty about potential efficacy in an intervention as yet untested in humans, and because of the design and goals of Phase I trials: dose escalation studies designed to elicit and examine toxicities, beginning at low doses unlikely to provide benefit to subjects even if the intervention worked perfectly (which it usually doesn't). Added to this was the concern that the parents of newborns in hyperammonemic crisis would be emotionally and informationally stressed, having just learned of the disorder because their child was gravely ill from it, and being asked to decide quickly about an unprecedented but emergent intervention. Aside from decision-making and consent issues and regulatory limitations on research with children (45 C.F.R. Part 46 Subpart D), all of which favored recruitment of adult subjects first, minimizing harm to subjects appeared to favor enrollment of newborns in crisis, since gene transfer was believed to pose low risks of harm and since these newborns were already seriously ill and already receiving maximal but suboptimal therapy. (Moreover, investigators and regulators alike were greatly tempted to reason that if this gene transfer worked, these babies could be saved.) In contrast, maximizing generalizable knowledge favored recruitment of partially affected, currently stable subjects. It would be very hard to determine, in newborns in acute crisis, which of any effects seen, whether for good or ill, resulted from the disease, the standard treatments, or the experimental intervention.

37. N.M.P. King, "Defining and Describing Benefit Appropriately in Clinical Trials," *Journal of Law, Medicine &Ethics,* 28, no. 4 (2000): 332-43.

38. See Rainsbury, *supra* note 2; statement of Dr. LeRoy Walters, *supra* note 8. Most recently, in response to questions raised about GTR oversight after Mr. Gelsinger's death, the Acting Director of NIH convened a working group from the standing Advisory Committee to the Director to critically examine the RAC's role and functions. See '½.dvisory Committee to the Director, Working Group on NIH Oversight of Clinical Gene Transfer Research, Enhancing the Protection of Human Subjects in Gene Transfer Research at the National Institutes of Health," July 12, 2000, *at* <http://www.nih.gov/about/director/07122000.htm> (last visited September 17, 2002). After the Advisory Committee to the Director Working Group issued its report, the RAC received authorization to expand its membership from fifteen, to add new relevant expertise in areas such as public policy and statistics.

39. This interview was conducted as one component of an Ethical, Legal, and Social Implications (ELSI) project, "The Social Construction of Benefit in Gene Transfer Research" (1 ROl HG 02087-01, ELSI Program, National Human Genome Research Institute, NIH). Gail E. Henderson and I are co-principal investigators, with co-investigators Larry R. Churchill, Arlene M. Davis, Daniel K. Nelson, and Benjamin S. Wilfond. The project also includes interviews with GTR investigators, study coordinators, and subjects, as well as review of nearly all consent forms and Points to Consider responses on file with OBA. Co-investigators Churchill, Nelson, and Wilfond conducted the IRB interviews between December 2000 and November 2001. The data presented here are preliminary results only.

40. Perhaps most common is some IRBs' reluctance to mention autopsy in the consent form, though Appendix M requires investigators to include in the consent form the information that permission for an autopsy of the subject will be requested from the next of kin at the time of the subject's death for any reason, in order to learn more about the long-term effects of GTR. Appendix M's discussion of autopsy requests thus addresses most IRBs' concerns, which include failure to appreciate the need for the information, worry that mentioning death might unduly alarm sick subjects, and fear that an autopsy request might be mistaken for an autopsy requirement; yet unless they read Appendix M, IRBs cannot discern this. Once the specific requirements that Appendix M places on investigators are drawn to the **IRB's** attention by OBA or the RAC, IRBs are, in my experience, very receptive to making suggested changes in consent forms.

41. Correspondence from OBA is sent to the principal investigator listed in OBA's files, and copied to the principal investigator's IRB. This means that in multicenter studies, the only IRB receiving correspondence is the IRB at the primary site - and even that IRB does not receive the attachments included in the letter to the principal investigator at the site. IRBs reviewing GTR thus must take additional steps in order to be most fully informed.

42. See D. Shalala, *supra* note 30; NIH, "Financial Conflicts of Interest and Research Objectivity," *supra* note 30; **NIH,** "Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials," #OD-00-038, June 2000, *at* <http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html> (last visited September 17, 2002); NIH, "Required Education in the Protection of Human Research Participants," #OD-00-039, June 2000, *at* <http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html> (last visited September 17, 2002).

43. 65 Fed. Reg. 60328-60332 (Oct. 10, 2000).

44. It is important that IRBs reviewing GTR become accustomed to requesting copies of Appendix M responses - from the principal investigator, OBA, or the IBC. Closer relationships between IRBs and IBCs are desirable as well, because IBCs usually do know about Appendix M, and may routinely review Appendix M responses from principal investigators - but many are unaccustomed to reviewing clinical research, and could learn much from the IRB.

45. Between 20 and 30 percent of protocols are selected for full public review and discussion, and that percentage is dropping as the number of protocols submitted to OBA for RAC review continues to grow.

46. S.G. Stolberg, "Agency Failed to Monitor Patients in Gene Research," *New York Ttmes,* Feb. 2, 2000, at 19.

47. 66 Fed. Reg. 57970-7 (Nov. 19, 2001). Final Paperwork Reduction Act clearance for adverse event reporting harmonization was given in March 2002.

48. 66 Fed. Reg. 57970-7 (Nov. 19, 2001). The Gene Transfer Safety Advisory Board (GTSAB) will have about fifteen members. Two will be members of the RAC. Members of the NIH staff will be included, as well as a FDA liaison. The remaining members will be chosen for their relevant expertise (e.g., scientific, clinical, statistical, ethical); *ad hoc* members will be involved as needed. The GTSAB will meet quarterly in closed session, and will provide summary reports to the RAC and for publication.

49. The Genetic Modification Clinical Research Information System (GeMCRIS) database is being developed by OBA in collaboration with the FDA and with input from all NIH institutes and centers that deal with gene transfer, as well as·the Clinical Center and the National Library of Medicine.

50. A range of documents, including listings and classifications of all open studies, is available on OBA's website. A limited, Phase I version of the GeMCRIS database is currently accessible *at* <http://www4.od.nih.gov/oba/rac/clinicaltrial.htm> (last visited September 17, 2002). It provides a range of information about current studies in a truncated searchable form.

51. Walters, *supra* note 2.

52. The appellation comes from Abbey Meyers, a former RAC member and a member of the recently disbanded National Human Research Protections Advisory Committee.

53. Rainsbury, *supra* note 2.

54. Churchill et al., *supra* note 20. As Churchill et al. have noted, somatic cell GTR has long been held to raise no new questions - but that does not mean that there are no old questions; in fact, there are many.

Submission #11

Name:	
Organization:	Biotechnology Innovation Organization
Email:	sramon@bio.org
Comment	Please see attached. Thank you.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	- - comment-form/uploads/FINAL_BIO Comments on NIH OSP Nucleic Acid Research_10-12-18.pdf

Biotechnology Innovation Organization

October 16, 2018

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

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)

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the National Institutes of Health (NIH) for the opportunity to submit comments regarding the Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO applauds the NIH's efforts to support and advance drug development for gene therapies. In particular through the streamlining of protocol registration and reporting requirements, and modification of the roles and responsibilities of the Recombinant DNA Advisory committee. As the NIH notes in the announcement, the goal is to eliminate duplication and excess as it related to gene therapy products regulation, redundancies that do not exist in most other areas of clinical research. BIO supports the comment made by the NIH indicating that, "oversight mechanisms for ensuring HGT [human gene transfer research] proceeds safely have sufficiently evolved to keep pace with new discoveries in this field." BIO believes that there is currently sufficient and robust regulatory framework in place for safe and effective development of gene therapy products.

We would like to note that in the Federal Notice, there is a requirement for an Institutional Biosafety Committee (IBC) approval from the study site before initiation of the study. However, many study sites do not have an established IBC. Therefore, this requirement could impede study initiation and enrolment as it takes a considerable amount of time to establish an IBC at the study site. Potential study sites could be dropped due to the inability to constitute an IBC. Hence, we respectfully propose that initiation of the study be allowed with Institutional Review Board (IRB) approval only at study sites where there are no IBCs. In addition, IBC may not have the same depth of experience when reviewing gene therapy protocols. We encourage the Agency to define more clearly the transfer of responsibilities, as well as the IBC review process

BIO appreciates this opportunity to submit comments regarding NIH's Recombinant or Synthetic Nucleic Acid Research: Proposed Changes to the NIH Guidelines for Research

Involving Recombinant or Synthetic Nucleic Acid Molecules. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

Submission #12

Name:	
Organization:	
Comment:	Rutgers, The State University of New Jersey welcomes the opportunity to comment on the proposed changes to the NIH Guidelines. The University supports some of the changes, but does so with the comments below. We believe that the changes will decrease redundancy and confusion between IBC and IRB review. Our specific comments are: RAC: The University's primary concern is regarding the removal of the RAC from the entire document, and doing so without including the revised mission or role of the RAC in an official manner. The change explains that the decisions previously made by RAC will now rest with the NIH Director and the OSP, especially regarding major actions. The regulatory change should use the opportunity of changing the regulations to delineate the new role and expectations of the RAC, and retain this long-standing committee in an official capacity. The mission of the RAC has been different than that originally intended in recent years, but the RAC is a valuable resource of experts that can be modified to reflect expertise in emerging technologies, drug resistance studies and other experiments where a deeper and transparent review is needed. The proposed changes indicate that the RAC will exist as an advisory body, but there are no other details to support or outline its revised mission. Additional detail is warranted and should be included in the final document. In July 2017, at the NIH workshop on the NIH Guidelines and their future, there was discussion about the RAC continuing review of emerging technologies, and drug resistant studies, and this would be the perfect opportunity to start that new effort. Appendix M: The specifics to Appendix M are very helpful in providing a guideline for investigators as to the considerations and explanations needed to assess these studies. The loss of this appendix as such a resource will be felt, but many IBCs may have incorporated these questions into their risk assessments. Many members of an IBC questioned the reason for reviewing consent documents because this created redundancy for work done by an IRB. The proposed regulatory change will permit the IBC to narrow its focus on worker safety and allow for thorough site specific review. This will also assist investigators in understanding the unique role of the IBC and the IRB and how to submit protocols for review to each. We do recommend retaining the content of Appendix M as a resource document. Finally, we strongly encourage the NIH Office of Science Policy to review the NIH guidelines to determine how to modify these guidelines in such a way to reflect the changing landscape of research in the age of genome editing while ensuring oversight and safety review. Also, including a mechanism for designated member review similar to IACUC or expedited review similar to IRB would enhance and streamline the review process.

	The University thanks you for reviewing its comment and considering them in the review of this important regulatory change.

Submission #13

Name:	
Organization:	
Comment:	As of August 26, 2018, 1,173 Institutional Biosafety Committees are registered with the NIH Office of Science Policy, covering risk assessments with recombinant and synthetic nucleic acid molecules under the NIH Guidelines. This represents a 59% increase since 2008, when 737 IBCs were registered (FOIA, 2018, 2008), in 24 countries, covering 6 continents. Most of these locations in the last 10 years, are clinical locations who review clinical applications of human gene transfer. In fact, there are more hospitals and clinics registered with the NIH Office of Science Policy then there are universities and clinics who review research in the more 'traditional manner' of pre-clinical cell culture and animal work, which has been reported by the NIH Office of Science Policy in past years, showcasing the rapid increase in the growth of this exciting clinical application. In addition, the risk assessments and their oversight in clinics and hospitals are vastly different than the application of the NIH Guidelines in pre-clinical cell and animal work. With an FDA IND in hand, the largest issues stem in pharmacy handling and clinical dosing of these therapeutics. For many locations, pharmacy and clinical staff have little to no experience on biosafety, disinfection, personal protective equipment, and engineering controls and view HGT akin to chemotherapy. This requires significant education, especially for replication competent biologicals being utilized. Many pharmacies and sponsors require additional handling procedures mid-study, and it would make sense to terminate IBC study oversight not when administration ends, but with the 3 criteria we typically use: 1) no product on site, 2) dosing is no longer occurring, and 3) trial is closed to enrollment. There is no question, as the NIH Director and FDA Commissioner specified, that gene therapy, gene transfer, and gene editing technologies have over the last 30 years moved the needle from being an emerging technology to emerged in their biotechnology and clinical applications. However, despite the advances, the additional expertise and viewpoints of the collective expertise on the RAC, was invaluable for the review of novel, complex technologies in the space. Recently, the emergence of CRISPR and CAR-T technologies open the door to a wide variety of clinical applications. However, we are still learning more about these technologies every day, from the cytokine release syndrome with CAR-T and potential off-target effects of CRISPR that are increasingly being reported. As trials increasingly move towards younger pediatric populations, and eventually, in utero, a body such as the RAC to review the ethical, scientific, and risk assessments in one review, is outside the FDA perview, and would remain beneficial. Respectfully, I believe novel technologies, should still have the ability by a local Institutional Biosafety Committee, to request review by the NIH

	Recombinant Advisory Committee. Many IBCs outside of the long-standing, academic medical centers who have traditionally been at the forefront of gene therapy, lack the expertise to adequately assess a risk assessment in clinical situations for handling in pharmacy and clinical setting. This comes from chairing hundreds of IBC meetings, reviewing hundreds of clinical protocols, and seeing exposures in the application of these trials to clinical, pharmacy, and family members. I recommend a process to recommend RAC review remain, with criteria similar to the April, 2016 Appendix M process, for local risk assessments by IBCs to request from NIH Office of Science Policy, to either the NIH OSP, or to a

Submission #14

Name:	
Organization:	McLean Hospital
Email:	PIBC@partners.org
Comment:	Jessica Tucker, Ph.D. 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) – Request for Comments Dear Dr. Tucker: Thank you for providing the research community with an opportunity to submit comments, as published in the Federal Register (FR) on August 17, 2018 on the proposed changes to NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines.) I am writing on behalf of McLean Hospital (McLean), a principal teaching affiliate of Harvard Medical School with a substantial research portfolio, and a member of the Partners HealthCare System. McLean maintains the largest program of research in neuroscience and psychiatry of any private psychiatric hospital in the US. In FY18, McLean received $49 million in research funding from federal and non-federal sources. We endorse the proposed changes to the NIH Guidelines. Reducing the regulatory burden on Principal Investigators and their clinical trials that use well-established products and technologies of recombinant and synthetic nucleic acid molecules will help accelerate the initiation of clinical trials and ensure compliance with existing regulations. While we generally agree with the proposed changes to Section III-C and the removal of Appendix L and Appendix M, and endorse these changes that removes Recombinant Advisory Committee (RAC) oversight of Human Gene Therapy (HGT) and HGT protocol reporting requirements to the Office of Science Policy (OSP), we do have several concerns and comments regarding these changes. First, we would appreciate clarification on the OSP view of the new role for the IBC in human subject research involving recombinant or synthetic nucleic acid molecules. Second, we would appreciate formal guidance on IBC

communication with federal agencies and other Institutions. Third, we would appreciate a clearer understanding the new role of the RAC and the NIH Guidelines with these changes. The RAC provides OSP and the NIH Director with valuable advice on current risks and trends in biological research and this expertise

The biomedical and life sciences have advanced significantly since the NIH Guidelines were first published. HGT experiments have matured to the point that it makes sense to review the oversight process, but we argue that other areas have also reach a level of maturity that would benefit from a similar review (e.g., as animal experiments and viral vector usage.) And though the NIH Guidelines have been revised multiple times, they do not address current trends and new risks posed to Institutional Biosafety Committees. Synthetic biology, CRISP-Cas9 technology, and gene drive experiments are areas that

• The OSP should perform a similar review of mature technologies covered under Section III-D and III-E of the NIH

• The NIH Director should update the RAC charter to ascertain current and future risks of leading-edge biological research and

With OSP no longer providing oversight at the federal level, IBCs are left without a federal point of contact to voice concerns identified during risk assessments. Appendix M provides clear guidelines for federal communication and risk assessments which would be lost. This potentially leaves IBCs disconnected from other IBCs and federal agencies in reporting identified risks and learning from other Institution's risk assessments. In

previous reviews of the clinical study. This is especially true in situations where an IBC declined to host a trial over of biosafety concerns as this may not be recorded in public IBC minutes, but would also include sharing best practices and mitigation

• Add language to the NIH Guidelines that requires sponsors of multisite human subject research trials to provide new sites a list of all sites that the trial was submitted to and previous IBC

The current changes are stated to align the review of recombinant and synthetic nucleic acid molecule research in humans with the current review of laboratory research. However, it is not clear what the OSP expects IBCs to review in

	a HGT trial. Current guidance for reviews found in Appendix M is being removed and supplemental guidance provided with the announcement suggest only reviewing shedding and administration. We would benefit from a clearer understanding of what a new HGT risk assessment would entail. This should include the aspects of the biological agent to review, what portion or the trial to review, containment levels, and what, if any, follow up review should be performed. The changes seem to imply that IBCs should no longer consider the risks of the biological agent itself (i.e. potential reversion to competent viral vector replication) or adverse events. Additionally, it is unclear what exposures to biological agents should be reported to OSP in the context of a clinical trial. For example, would reportable incidents include potential exposure between human subjects and close contacts? Finally, supplemental guidance with these changes suggests that review should stop at administration despite the potential for risks in biological specimens taken from subjects after the final administration. Recommendations: • The OSP should provide guidance on the Risk Assessment process and containment levels for HGT trials. • The OSP should clarify if adverse events and significant adverse events should be reported to the IBC. • The OSP should clarify if exposure in the clinical setting is reportable. • The OSP should clarify what types of clinical protocol amendments should be submitted to the IBC. • The OSP should clarify at what point the IBC review of a trial is complete. It is our belief that local oversight by Institutional Biosafety Committees and Institutional Review Boards of biomedical research has been effective at ensuring the safety of the community and environment, clinical staff, and human subjects and will continue to do so. Reducing the regulatory burden will contribute to timely transition of gene therapy products into clinical trials. I greatly appreciative the opportunity to provide the OSP with these comments regarding the proposed changes to the NIH Guidelines. Yours sincerely, Kerry Ressler, MD, PhD Chief Scientific Officer McLean Hospital
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/McLean NIH Gildelines Comments.pdf

Jessica Tucker, Ph.D.
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*) – Request for Comments

Dear Dr. Tucker:

Thank you for providing the research community with an opportunity to submit comments, as published in the Federal Register (FR) on August 17, 2018 on the proposed changes to *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (N*IH Guidelines.*) I am writing on behalf of McLean Hospital (McLean), a principal teaching affiliate of Harvard Medical School with a substantial research portfolio, and a member of the Partners HealthCare System. McLean maintains the largest program of research in neuroscience and psychiatry of any private psychiatric hospital in the US. In FY18, McLean received $49 million in research funding from federal and non-federal sources.

We endorse the proposed changes to the *NIH Guidelines*. Reducing the regulatory burden on Principal Investigators and their clinical trials that use well-established products and technologies of recombinant and synthetic nucleic acid molecules will help accelerate the initiation of clinical trials and ensure compliance with existing regulations.

While we generally agree with the proposed changes to Section III-C and the removal of Appendix L and Appendix M, and endorse these changes that removes Recombinant Advisory Committee (RAC) oversight of Human Gene Therapy (HGT) and HGT protocol reporting requirements to the Office of Science Policy (OSP), we do have several concerns and comments regarding these changes. First, we would appreciate clarification on the OSP view of the new role for the IBC in human subject research involving recombinant or synthetic nucleic acid molecules. Second, we would appreciate formal guidance on IBC communication with federal agencies and other Institutions. Third, we would appreciate a clearer understanding the new role of the RAC and the NIH Guidelines with these changes.

The RAC provides OSP and the NIH Director with valuable advice on current risks and trends in biological research and this expertise should be retained.

The biomedical and life sciences have advanced significantly since the *NIH Guidelines* were first published. HGT experiments have matured to the point that it makes sense to review the oversight process, but we argue that other areas have also reach a level of maturity that would benefit from a similar review (*e.g.,* as animal experiments and viral vector usage.) And though the *NIH Guidelines* have been revised multiple times, they do not address current trends and new risks posed to Institutional Biosafety Committees. Synthetic biology, CRISP-Cas9 technology, and gene drive experiments are areas that would benefit from guidance from the OSP and the RAC.

Recommendations:

- The OSP should perform a similar review of mature technologies covered under Section III-D and III-E of the *NIH Guidelines*.
- The NIH Director should update the RAC charter to ascertain current and future risks of leading-edge biological research and provide OSP guidance in those areas.

With OSP no longer providing oversight at the federal level, IBCs are left without a federal point of contact to voice concerns identified during risk assessments. Appendix M provides clear guidelines for federal communication and risk assessments which would be lost. This potentially leaves IBCs disconnected from other IBCs and federal agencies in reporting identified risks and learning from other Institution's risk assessments. In multisite trials, it would be useful for an IBC to have access to previous reviews of the clinical study. This is especially true in situations where an IBC declined to host a trial over of biosafety concerns as this may not be recorded in public IBC minutes, but would also include sharing best practices and mitigation strategies for the trial.

Recommendations:

- Add language to the NIH Guidelines that requires sponsors of multisite human subject research trials to provide new sites a list of all sites that the trial was submitted to and previous IBC approval letters.

The current changes are stated to align the review of recombinant and synthetic nucleic acid molecule research in humans with the current review of laboratory research. However, it is not clear what the OSP expects IBCs to review in a HGT trial. Current guidance for reviews found in Appendix M is being removed and supplemental guidance provided with the announcement suggest only reviewing shedding and administration. We would benefit from a clearer understanding of what a new HGT risk assessment would entail. This should include the aspects of the biological agent to review, what portion or the trial to review, containment levels, and what, if any, follow up review should be performed. The changes seem to imply that IBCs should no longer consider the risks of the biological agent itself (i.e. potential reversion to competent viral vector replication) or adverse events. Additionally, it is unclear what exposures to biological agents should be reported to OSP in the context of a clinical trial. For example, would reportable incidents include potential exposure between human subjects and close contacts? Finally, supplemental guidance with

these changes suggests that review should stop at administration despite the potential for risks in biological specimens taken from subjects after the final administration.

Recommendations:

- The OSP should provide guidance on the Risk Assessment process and containment levels for HGT trials.
- The OSP should clarify if adverse events and significant adverse events should be reported to the IBC.
- The OSP should clarify if exposure in the clinical setting is reportable.
- The OSP should clarify what types of clinical protocol amendments should be submitted to the IBC.
- The OSP should clarify at what point the IBC review of a trial is complete.

It is our belief that local oversight by Institutional Biosafety Committees and Institutional Review Boards of biomedical research has been effective at ensuring the safety of the community and environment, clinical staff, and human subjects and will continue to do so. Reducing the regulatory burden will contribute to timely transition of gene therapy products into clinical trials.

I greatly appreciative the opportunity to provide the OSP with these comments regarding the proposed changes to the NIH Guidelines.

Yours sincerely,

Kerry Ressler, MD, PhD
Chief Scientific Officer
McLean Hospital

Submission #15

Name:	
Organization:	Massachusetts General Hospital
Email:	PIBC@partners.org
Comment:	Jessica Tucker, Ph.D. 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) – Request for Comments Dear Dr. Tucker: Thank you for providing the research community with an opportunity to submit comments, as published in the Federal Register (FR) on August 17, 2018 on proposed changes NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines.) I am writing on behalf of Massachusetts General Hospital (MGH), a principal teaching affiliate of Harvard Medical School with a substantial research portfolio. In FY18, MGH was ranked first among hospitals receiving NIH funding support and received $928 million in research funding from federal and non-federal sources. We endorse the proposed changes to the NIH Guidelines. Reducing the regulatory burden on Principal Investigators and their clinical trials that use well-established products and technologies of recombinant and synthetic nucleic acid molecules will help accelerate the initiation of clinical trials and ensure compliance with existing regulations. While we generally agree with the proposed changes to Section III-C and the removal of Appendix L and Appendix M, and endorse these changes that removes Recombinant Advisory Committee (RAC) oversight of Human Gene Therapy (HGT) and HGT protocol reporting requirements to the Office of Science Policy (OSP), we do have several concerns and comments regarding these changes. First, we would appreciate clarification on the OSP view of the new role for the IBC in human subject research involving recombinant or synthetic nucleic acid molecules. Second, we would appreciate formal guidance on IBC communication with federal agencies and other Institutions. Third, we would appreciate a clearer understanding the new role

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Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/MGH NIH Gildelines Comments.pdf

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Harry W. Orf, Ph.D
Senior Vice President for Research
Massac/msetts General Hospital
Principal Associate i11 Genetics
Harvard Medical School

October 12, 2018

Jessica Tucker, Ph.D.
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)* - Request for Comments

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Harry W. Orf, Ph.D
Senior Vice President for Research
Massachusetts General Hospital

P.AR:rNEiffi.
HealthCare

Submission #16

Name:	
Email:	
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BRIGHAM AND WOMEN'S HOSPITAL

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Paul J. Anderson, M.D., Ph.D.
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October 12, 2018

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Chief Academic Officer
Brigham and Women's Hospital

Submission #17

Name:	Christopher Porada
Organization:	IFeTIS
Email:	cporada@wakehealth.edu
Comment:	Please see attached letter
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	- - comment-form/uploads/iFeTIS letter for FDA 10_13_18.pdf

Christopher Porada, PhD
IFeTis President elect
Professor of Regenerative Medicine
Member, Center for Genomics & Personalized Medicine
University Wake Forest Institute for Regenerative Medicine
Wake Forest School of Medicine
391 Technology Way
Winston Salem, NC 27157-1083

October 13th 2018

The International Fetal Transplantation and Immunology Society (IFeTIS) promotes basic and translational research leading to the development of fetal therapies, and raises public and scientific awareness of the need for development of fetal treatments.

We are submitting this letter to convey our support of the NIH proposal to revise the 'Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules' in order to streamline oversight for human gene transfer research. Great scientific progress has been made in the last decade, and the current guidelines do not reflect the knowledge or the societal acceptance of the field. As such, they create unnecessary burdens and greatly complicate reporting practices.

IFeTIS supports the proposed amendments, since they will foster new clinical trials in this important area without forgoing of quality or patient safety.

The main objective of IFeTIS is to accelerate clinical applications of stem cell transplantation and gene therapy to treat fetuses with congenital disorders; therefore, we are also expressing our support for revising the guidelines for in utero gene therapy (IUGT), since this approach is emerging as an important clinical option for treating genetic disorders that can be diagnosed prenatally. Therefore, we urge you to incorporate this area as you consider the upcoming modifications of genetic therapies.

On June 11-12, 2018 IFeTIS facilitated a panel discussion of international experts considering scientific, clinical, and ethical issues related to prenatal gene transfer for the treatment of genetic diseases. The consensus of this panel of experts was that IUGT has the vast and unique potential for dramatically improving the standard of care for many patients with genetic disorders (document in preparation for press release).

Gene delivery and therapy technologies have evolved significantly in the last decade, such that many of the most daunting obstacles have now better been identified. As a result, this exciting field has been reinvigorated. There is no doubt that surpassing the few remaining hurdles to allow clinical implementation of these therapies is urgently needed, and that IUGT will dramatically change the whole paradigm for the way we perceive and treat many genetic disorders. IFeTIS members agreed that one of the main goals of prenatal therapy should be to induce tolerance to the missing protein and/or prevent damage caused by the disease during development. In addition, we recognized that the unique physiologic characteristics of the fetus, such as the more permissive blood-brain barrier, may make possible successful delivery to otherwise difficult-to-

access tissues. As such, ideal diseases to target would be those that result in severe fetal morbidity and/or mortality either in utero or post-natally and/or those for which available post-natal treatments are hindered by immunologic responses/rejection.

We also acknowledged that outcomes and parameters of success for post-natal gene therapy in infants and children may not correlate with those for IUGT, and as such, specific studies using avatars able to model fetal development should be performed.

Above all, IFeTIS recognized that maternal safety is a critical consideration for IUGT, and that protection of the physical safety and emotional well-being of the mother is a must.

Nevertheless, data from clinical drug trials shows that pregnant women constitute an underrepresented population, which has created a potentially dangerous gap in knowledge regarding appropriate management of this group. Thus, the mechanisms of assessment of risk/benefit should be updated and simplified to incentivize greater and better research during pregnancy, so that the opportunity to enhance the health and safety of pregnant women and infants is not neglected.

We wish to thank the FDA for acknowledging the need to update the now outdated guidelines governing gene therapies, and for its time and consideration in reviewing our comments. We eagerly await seeing your final revisions to these important guidelines.

Respectfully yours, on behalf of IFeTIS,

Christopher Porada, PhD
IFeTis President elect
Professor of Regenerative Medicine
Member, Center for Genomics & Personalized Medicine
University Wake Forest Institute for Regenerative Medicine
Wake Forest School of Medicine
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Associate Professor of Surgery
Director, Center for Maternal-Fetal Precision Medicine
Email: tippi.mackenzie@ucsfmedctr.org

IFeTis Board of Directors

Submission #18

	10/15/2018
Name:	Ellyn Segal
Organization:	Stanford University
Email:	esegal@stanford.edu
Comment:	Please see attached correspondence from Stanford University regarding proposed changes to RAC and NIH Guidelines.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/Final.pdf

STANFORD UNIVERSITY

ENVIRONMENTAL HEALTH & SAFETY

Biosafety Program

Ellyn Segal, Ph.D.
Biosafety Manager

Oct. 15, 2018

Re: Proposal to Streamline Review of Gene Therapy Trials and Restore the Original Vision of the RAC

To Whom It May Concern:

The recent proposal by the NIH (https://www.federalregister.gov/documents/2018/08/17/2018-17760/national-institutes-of-health-nih-office-of-science-policy-osp-recombinant-or-synthetic-nucleic-acid) was proposed to "…streamline oversight (re NIH/FDA) by eliminating unnecessary duplicative reporting requirements" specifically targets human gene therapy clinical trials (HGT). This amendment includes:

1. Elimination of RAC review and reporting requirements to NIH for HGT protocols.
2. Modification of roles and responsibilities of investigators, institutions, IBCs, the RAC, and NIH to be consistent with these goals including:

    a. Modifying roles of IBCs in reviewing HGT to be consistent with review of other covered research, and
    b. Eliminating references to the RAC, including its roles in HGT and biosafety.

Per NIH (J. Tucker, Director, Division of Biosafety, Biosecurity, and Emerging Biotechnology Policy, Office of Science Policy) implementation of these amendments would have the following downstream effects:

1. IBC oversight should be completed immediately after the last participant is administered the final dose of product
2. IBC oversight will be restricted to review of product (rDNA) administration and shedding; the IBC will no longer have input on documents such as the Informed Consent or safety reporting.

NIH put forth that the present model of HGT review produces duplication in reviews and paperwork, with both the NIH and FDA currently requiring initial registration of HGT protocols and updates as the study proceeds; this is not required of any other field of clinical research.

This premise begs the following question: do any differences between HGT and traditional FDA oversight products warrant the potential duplication of effort? HGT is unique as it uses molecules that, by nature, can both replicate within a human outside of the genome or can insert within the genome with the potential to produce permanent genetic changes related to gene expression.

The concern over research using rDNA is the reason that the rDNA Guidelines came about. It was realized at that time (over 40 years ago) that the use of DNA did warrant additional oversight; while it is extremely satisfying that research with rDNA has evolved into FDA approved therapies this does not negate the inherent and intrinsic issues related to use of DNA in humans. Yes, in 2017 the FDA approved three HGT products for use in the United States, one of which acts by targeting a specific genetic condition (retinal dystrophy) and two which are cell-based therapies (Car-T). None of the aforementioned products involve the newest technical component - CRISPR, which is just going into clinical trials. Science

is still learning and being surprised on how genes interact and function - research should not become complacent about potential effects. Progress in technology brings new questions and concerns, i.e. potential off-target effects of CRISPR or cytokine release syndrome associated with CAR-T procedures. It does seem reasonable that a day will come when HGT is a mainstay of treatment for many diseases; this day is not yet here, nor are we ready to decrease oversight as the field grows and learns. To provide decreased oversight of such research would be a disservice to both science and subjects.

To support the revisions NIH stated (www.nejm.org/doi/pdf/10.1056/NEJMp1810628) that oversight of HGT trials has evolved and point to the ClinicalTrials.gov database, which NIH proposes to fill the void left by removing the functionality of the IBC review process. The database is useful for subjects to identify actively recruiting or upcoming studies. The database does not function as a replacement for expert review and oversight of projects, either at the start or during a study, nor justify removal of a technical expert panel for safety event review. The NIH US National Library of Medicine, on the ClinicalTrials.gov web site, states the following (italics are the authors):

https://clinicaltrials.gov/ct2/about-site/disclaimer

> Disclaimer
>
> Listing a study on this site does not mean it has been evaluated by the U.S. Federal Government. *The safety and scientific validity of a study listed on ClinicalTrials.gov is the responsibility of the study sponsor and investigators*. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating.
>
> ClinicalTrials.gov, a resource provided by the U.S. National Library of Medicine (NLM), is a registry and results information database of clinical research studies sponsored or funded by a broad range of public and private organizations around the world. Not all studies listed on ClinicalTrials.gov are funded by the National Institutes of Health (NIH) or other agencies of the U.S. Federal Government. Not all listed studies are regulated and/or reviewed by the U.S. Food and Drug Administration or other governmental entities.
>
> Information on ClinicalTrials.gov is provided by study sponsors and investigators, and they are responsible for ensuring that the studies follow all applicable laws and regulations*. NLM staff do not verify the scientific validity or relevance of the submitted information beyond a limited quality control review for apparent errors, deficiencies, or inconsistencies*.

Given that the NIH recognizes areas lacking in ClinicalTrials.gov, it is not reasonable to suggest that the database substitute for oversight by RAC/IBCs.

Suggestions

It is reasonable to acknowledge the growth of experience and knowledge in the field of HTG, and to extend this growth into a streamlined review process; this action was accomplished in April 2016 by the decision tree re-design for protocols needing RAC review. To continue the level of review and oversight HGT necessitates it is suggested

1. to leave RAC review as it currently stands, with a minority of HGT protocols representing novel technologies being subjected to input from RAC (post implementation of review triage in 2016 only 3 out of 275 protocols were deemed to warrant RAC review (www.nejm.org/doi/pdf/10.1056/NEJMp1810628));

2. retain IBC input and review of HGT protocols as it currently exists

Historically an IBC would supply the technical expertise for these reviews (as based on the rDNA Guidelines recommendations). As such, an IRB would concentrate on staffing experts in more traditional fields of human medical trials. It can be challenging to identify such experts to fulfill HGT oversight roles, especially in smaller institutions and clinical sites. If the proposed changes in IBC function come about HGT experts will continue to be needed on IBCs for initial review and also be needed on IRBs for continuing review responsibilities; this will lead to increased burden on numerous IBCs. In summary it is strongly suggested that if RAC review does not remain available, it will be even of greater importance to have IBC input and review present throughout the life of a HGT study.

Thank you for your time and consideration in this matter.

Sincerely,

Mark Holodniy, MD, FACP, FIDSA
Chair, Institutional Biosafety Committee
Professor of Medicine – Med/Infectious Diseases
Stanford University

Yvonne Maldonado, MD
Co-Chair, Institutional Biosafety Committee
Senior Associate Dean, Faculty Development and Diversity
Professor of Pediatrics – Infectious Diseases and of Health Research and Policy
Stanford University

Ellyn Segal, Ph.D.
Assistant Director, Biosafety and Biosecurity
Environmental Health and Safety
Stanford University

Submission #19

Comment:	October 15, 2018 Jessica Tucker, Ph.D. Office of Science Policy National Institutes of Health 6705 Rockledge Drive, Suite 750 Bethesda, MD 20892 Dear Dr. Tucker, The University Washington is submitting the these comments in response to the notice in the Federal Registry dated August 16th, 2018 inviting comment on the proposed notice to amend the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines). We applaud the NIH for making changes to reduce duplication of clinical trial protocol reporting to both the NIH and FDA for human gene transfer (HGT) research. We encourage the NIH to continue to seek ways to enhance efficiency and reduce administrative burden when there is not a proportional safety benefit where possible. We support the NIH's vision of using the RAC as an advisory board for emerging biotechnologies, such as gene editing, synthetic biology, and neurotechnology. There is no entity at the NIH and specifically the OSP that is tasked with a role similar to that carried out by the RAC. The proposed change in the role of the RAC to no longer review specific projects will place additional responsibility on the local IBCs to conduct the biosafety review with appropriate subject matter expertise on the proposed technology and methods. More clear and specific guidance is needed about what an IBC review of a human gene transfer trial should include and about the responsibilities of the local IBCs. The proposed wording for Section IV-B-2-b-(1) "(iii) for recombinant or synthetic nucleic acid molecule research involving human research participants, assessment focused on biosafety issues (e.g., administration, shedding)" does not provide enough information about the exact scope of the IBC's review. In the absence of official RAC review, a point of contact at OSP should be appointed that can assist in providing guidance, knowledge, or referral to subject matter experts would be extremely beneficial. The point of contact must

be an individual(s) that has a robust background in pre-clinical or clinical HGT. The questions in the Appendix M are very beneficial to the IBC review of the biosafety risks and they should continue

In addition, IBCs would benefit if the NIH could provide a mechanism for sharing findings during IBC reviews for HGT research. Many HGTs are multisite trials reviewed by many different IBCs and it would be ideal to have a way to share information to assist with questions that IBC reviewers may have

Summary of Comments and Recommendations:
• We are in support of the NIH proposal to reduce duplicative reporting requirements for human gene transfer protocols.
• Identify a point of contact at OSP that is a subject matter expert in clinical HGT research or create a panel of experts to address questions and provide appropriate technical guidance for all inquiries on HGT.
• Provide more clarity and detail about what the scope and level of an IBC HGT review should be and explicitly state the responsibilities of the IBC for HGT.
• Review and update the NIH Guidelines to provide more relevant and up to date guidance and clarity for IBCs to assist with their

• Continue to require that the Appendix M level details be

Thank you for the opportunity to provide input on this very important rulemaking effort. We are happy to answer questions

Stephen Libby, Ph.D.
Institutional Biosafety Committee Chair

Zara Llewellyn, Ph.D., RBP
Biosafety Manager
Environmental Health & Safety Department

Assistant Director for Research and Occupational Safety
Environmental Health & Safety Department
University of Washington

Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/UW_NIH_Comment Letter_Gene Therapy Trials.pdf

October 15, 2018

Jessica Tucker, Ph.D.

Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Dr. Tucker,

The University Washington is submitting the these comments in response to the notice in the Federal Registry dated August 16th, 2018 inviting comment on the proposed notice to amend the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines). We applaud the NIH for making changes to reduce duplication of clinical trial protocol reporting to both the NIH and FDA for human gene transfer (HGT) research. We encourage the NIH to continue to seek ways to enhance efficiency and reduce administrative burden when there is not a proportional safety benefit where possible.

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More clear and specific guidance is needed about what an IBC review of a human gene transfer trial should include and about the responsibilities of the local IBCs. The proposed wording for Section IV-B-2-b-(1) *"(iii) for recombinant or synthetic nucleic acid molecule research involving human research participants, assessment focused on biosafety issues (*e.g., *administration, shedding)"* does not provide enough information about the exact scope of the IBC's review. In the absence of official RAC review, a point of contact at OSP should be appointed that can assist in providing guidance, knowledge, or referral to subject matter experts would be extremely beneficial. The point of contact must be an individual(s) that has a robust background in pre-clinical or clinical HGT. The questions in the Appendix M are very beneficial to the IBC review of the biosafety risks and they should continue to be required for IBCs to address in their review.

In addition, IBCs would benefit if the NIH could provide a mechanism for sharing findings during IBC reviews for HGT research. Many HGTs are multisite trials reviewed by many different IBCs and it would be ideal to have a way to share information to assist with questions that IBC reviewers may have about the research.

Summary of Comments and Recommendations:

- We are in support of the NIH proposal to reduce duplicative reporting requirements for human gene transfer protocols.
- Identify a point of contact at OSP that is a subject matter expert in clinical HGT research or create a panel of experts to address questions and provide appropriate technical guidance for all inquiries on HGT.
- Provide more clarity and detail about what the scope and level of an IBC HGT review should be and explicitly state the responsibilities of the IBC for HGT.
- Review and update the NIH Guidelines to provide more relevant and up to date guidance and clarity for IBCs to assist with their HGT.
- Provide a mechanism for IBC reviews from different clinical trial sites to be shared.
- Continue to require that the Appendix M level details be included with the IBC review.

Thank you for the opportunity to provide input on this very important rulemaking effort. We are happy to answer questions or provide additional information about our recommendations.

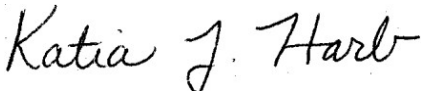
Sincerely,

Stephen Libby, Ph.D.

Institutional Biosafety Committee Chair
Research Associate Professor
Laboratory Medicine University of Washington

Zara Llewellyn, Ph.D., RBP

Biosafety Manager
Environmental Health & Safety Department
University of Washington



Katia Harb, MS, RBP

Interim Senior Director
Assistant Director for Research and Occupational Safety
Environmental Health & Safety Department
University of Washington

Submission #20

Date	10/15/2018
Name:	Cassandra Lucas
Organization:	Stanley Manne Children's Research Institute
Email:	clucas@luriechildrens.org
Comment:	The Stanley Manne Children's Research Institute fully supports the position and recommendations of the American Biological Safety Association regarding the changes to the "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)" published 17 August 2018. As a pediatric institution, we recommend continued RAC review prior to first-in-human/Phase I trials and particularly before enrolling children in human gene therapy trials.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/NIH_StanleyManneChildrensResearchInstitute.pdf

Stanley Manne
Children's Research Institute™

October 15, 2018

National Institutes of Health
Office of Science Policy

Re: Comments on the proposed changes *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*

To Whom It May Concern

The Stanley Manne Children's Research Institute fully supports the position and recommendations of the American Biological Safety Association regarding the changes to the "*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*)*" published 17 August 2018.

As a pediatric institution, we recommend continued RAC review prior to first-in-human/Phase I trials and particularly before enrolling children in human gene therapy trials.

Thank you in advance for your consideration.

Sincerely,

Cassandra L. Lucas, PhD, CRA
Chief Operating Officer and Institutional Official
Stanley Manne Children's Research Institute
Ann & Robert H. Lurie Children's Hospital of Chicago
T 773.755.6301 | F 773.755.6533 | clucas@luriechildrens.org | www.luriechildrensresearch.org
225 East Chicago Avenue, Box 205, Chicago, Illinois 60611-2991

Submission #82

Name:	
Email:	
Comment:	Elimination of the NIH RAC review: Concern: Eliminating the Recombinant DNA Advisory Committee (RAC) from performing a transparent and scientific review of Human Gene Transfer (HGT) clinical trials is of great concern and deemed inadvisable. Removing the RAC, a body of world-class experts, from being an integrated and defined component of NIH research oversight for recently emerged and emerging technologies has a negative impact on the safe conduct of research. Recommendation: Continue RAC review for emerging and recently emerged technologies, for Phase I and first in human use research, for decisions regarding major actions, and for monitoring incident reports. Use this opportunity to detail a process for the NIH Director, and for Institutional Biosafety Committees (IBC) and investigators to solicit input from this committee of world-class experts. Revise the NIH Guidelines, the RAC Charter, and other pertinent documents accordingly and release for public review and comment.

Submission #83

	10/15/2018
Name:	Esmeralda Meyer
Organization:	Emory University
Email:	evargas@emory.edu
Comment:	Elimination of the NIH RAC review: Concern: Elimination of the questions and documents required under Appendix M: Concern: Appendix M contains questions and document requirements that are used by the biosafety professional to conduct the initial risk assessment of using a recombinant or synthetic nucleic acid in a clinical trial. This will prompt a pushback from sponsors who usually provide the documents and respond to questions such as who will conduct the replication competency tests for the biological product used in the study. Sponsors will elegantly point that such information is not needed. The recommendation would be to include language enabling the IBC to request documentation and information needed to conduct the risk assessment and IBC review.

Submission #84

Name:	
Organization:	
Comment:	The following criteria that currently prompts NIH RAC review and that are proposed to be deleted could be added to the section III-A-1 Major Actions : The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk. The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value. The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate the protocol rigorously. These are critical elements that should trigger NIH review once the IBC has made the initial determination.

Submission #85

Name:	
Organization:	Alliance for Regenerative Medicine
Email:	
Comment:	
extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	comment-form/uploads/NIH-RAC Comments FINAL 10 15 18.docx

October 15, 2018

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

The following are comments from the Alliance for Regenerative Medicine (ARM) in response to the policy ("the policy") published in the Federal Register on August 17, 2018 entitled "Recombinant or Synthetic Nucleic Acid Research: Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines).

ARM is the leading international organization advocating for policies to support research and commercialization of regenerative medicine, cell and gene therapy, and other advanced therapies. Its more than 300 members include life sciences companies, research institutions, clinical centers, patient advocacy groups, and investors.

Since its inception, ARM has worked with the NIH to promote research and eventual commercialization of gene therapy. ARM has previously supported the Recombinant DNA Advisory Committee (RAC) in its mission to publicly discuss novel technologies. ARM has also expressed concerns with the duplicative nature of RAC review and reporting requirements.

Consequently, ARM strongly supports for the policy detailed by the NIH in the policy. Specifically, ARM welcomes the changes to NIH Guidelines that no longer require submissions to the RAC for gene therapy clinical trials. Gene therapy research and clinical development have become more prevalent in the last 40 years and the understanding of the complex scientific, ethical, and legal issues related to recombinant DNA technology has grown as well. The RAC was initially created because of the novelty of gene transfer and concerns about public acceptance and understanding of the technology.

This is no longer true. Several gene therapy products have now been approved by the US Food and Drug Administration. ARM has previously noted that gene therapy has significantly advanced since the establishment of the RAC, and Institutional Biosafety Committees (IBCs) have sufficient expertise and experience to ensure patient safety.

In addition, with hundreds of trials underway – many in later stages – the FDA knowledge of gene transfer and related technologies provides appropriate oversight. FDA has issued over a dozen guidance documents on the development of cell and gene-based therapies, including several in the last year. Additional review from the RAC is no longer needed. The review and

data reporting requirements as previously required by NIH Guidelines were duplicative and ARM is pleased that NIH has removed them from its guidelines.

We were also pleased to see that the policy maintains an ongoing role for the RAC. ARM supports the role of the RAC as a public forum to advise on issues related to new biotechnologies. For example, ARM would endorse RAC efforts to organize scientific workshops on gene therapy, particularly for novel approaches.

In addition, ARM recommends that the RAC clarify the role of IBCs going forward. The RAC should consider providing general guidance for IBCs (including potentially templates such as shortened/simplified Appendix M.). We anticipate this will be particularly helpful for IBCs that do not have a lot of experience with gene therapy.

ARM has previously expressed concern about the confidentiality of data provided to the RAC. Since commercial sponsors will no longer be required to report to the RAC nor have individual protocols reviewed, we anticipate this concern no longer applies. ARM encourages the NIH/RAC to clarify it will no longer require such information. However, due to the previous policy, the RAC remains in possession of trade secret and confidential commercial information. RAC should clarify that it will notify sponsors if any of their data may become publicly available.

ARM looks forward to continuing to work with the NIH/RAC to foster research in gene therapy and related technologies.

Respectfully,

Director, U.S. Policy and Advocacy

Submission #25

Name:	Tippi Mackenzie
Organization:	University of California at San Francisco
Email:	Tippi.Mackenzie@ucsf.edu
Comment:	October 15, 2018 Office of Science Policy National Institutes of Health 6705 Rockledge Drive, Suite 750 Bethesda, Maryland 20892 Re: Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) To Whom It May Concern: We are a team of clinicians, researchers, and bioethicists from the UCSF Center for Maternal-Fetal Precision Medicine and the Program on Bioethics. We submit these comments to communicate our support of the recent proposal by the NIH to amend the 'Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules' in order to streamline oversight for human gene transfer research. The 2014 Institute of Medicine report1 that informed these proposed amendments concluded that much of the science of gene transfer research has advanced significantly and is no longer novel or requiring special/public oversight by the RAC. The current guidelines are a remnant of an earlier era and create unnecessary burdens and complicated reporting practices. We believe the proposed amendments will increase clinical trials in this important area without sacrificing quality, safety, or appropriate oversight. We agree that the vast majority of somatic gene transfer research and gene therapy trials do not require additional review by the RAC and they need not be treated as an exceptional category of research. We are writing to express our support for revising the guidelines and note that in utero gene therapy (IUGT) is likely to emerge as an important clinical modality in treating genetic disorders that can be diagnosed prenatally. We urge you to include specific consideration of this area as you refine and implement changes to the guidelines. We at the UCSF Center for Maternal-Fetal Precision Medicine are conducting translational and clinical research on fetal therapy for different rare genetic disorders. Our team of clinicians, researchers, bioethicists, and patient advisors is conducting the first FDA approved phase I clinical trial of an in utero stem cell

transplantation protocol for fetal alpha thalassemia major. We are also members of the International Fetal Transplantation and Immunology Society (IFETIS), a group of scientists and clinicians focused on developing safe and effective prenatal therapies. In utero gene therapy offers numerous potential advantages over postnatal treatments as outlined extensively in the field.2 The unique immunological state of the fetus allows the ability to induce tolerance to missing proteins, thus circumventing one of the most important issues with postnatal replacement. There may be additional benefits in being able to treat neurological diseases before the blood brain barrier forms. Finally, in utero therapy may be effective in treating severe diseases that cause in utero or early postnatal demise, or progressive organ damage that begins in

We believe that there are important criteria that should be carefully assessed when evaluating in utero gene therapy trials.

1. Accurate prenatal diagnosis with a good understanding of the genotype/phenotype correlation affecting clinical prognosis.
2. Maternal safety: While preclinical studies of IUGT have not

safety concerns for mothers, an assessment of maternal exposure should be a part of clinical IUGT programs.
3. Fetal safety: One of the goals of prenatal therapy is to induce

the missing protein and clinical efforts should specifically measure this response, when relevant. Notably, tolerance to the

vector has not been seen in preclinical studies. Germline integration
has also not been observed in preclinical studies but must be

the clinical assessment when possible.
4. Assessment of ethical issues around potential coercion, non-

counseling, and partial treatment of a fatal disease
5. Involvement of multidisciplinary teams with specific local expertise in
fetal surgery/therapy, genetics, and bioethics.
6. Robust community engagement programs with potential participants in
order to integrate participant perspectives throughout the research

Pregnant women are underrepresented in all clinical trials for a variety of reasons, including increased regulatory scrutiny. Efforts to protect these vulnerable populations have resulted in knowledge gaps for providers regarding appropriate management of these patients, with pharmaceuticals being a prime example. While we agree that we need specific risk/benefit assessments and

considerations when conducting research during pregnancy, these mechanisms must be streamlined and simplified to incentivize greater research during the prenatal period. Without this important research, we are missing out on a vital opportunity to enhance the

Given the complexity of IUGT research, it is essential to have multiple types of expertise on the team, informing and participating in all aspects of the project. This research (like all innovative research) requires careful consideration of the clinical, ethical, scientific, psychosocial, and societal implications throughout the design and implementation. The institutional or external review process is important but cannot replace the role of ethics expertise and patient/participant involvement on the team

Finally, we support the language in the amendment, modifying the roles of institutional biosafety committees (IBCs) to ensure that they are responsible for reviewing human gene trials. We request

have the appropriate scientific and ethical expertise necessary for providing comprehensive oversight of all gene therapy trials. We believe the RAC should still serve an important role in training and

Tippi MacKenzie, MD Julie Harris-Wai, PhD MPH
Professor of Surgery Assistant Professor of
tippi.mackenzie@ucsf.edu Bioethics
-

Mary Norton, MD Barbara Koenig, PhD
Professor of Obstetrics, Gynecology, Professor and Director
and Reproductive Sciences Program on Bioethics

Billie Lianoglou, MS, LCGC
-

1. Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee. Committee on the Independent Review and Assessment of the

the NIH Recombinant DNA Advisory Committee, Board on Health Sciences Policy, Institute of Medicine; Lenzi RN, Altevogt BM, Gostin LO,

	editors. Washington (DC): National Academies Press (US); 2014 Mar 27. 2. MacKenzie Tippi C. Future AAVenues for In Utero Gene Therapy. Cell Stem Cell. 2018 Sep 6;23(3):320-321.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	- - -

October 15, 2018

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

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

To Whom It May Concern:

We are a team of clinicians, researchers, and bioethicists from the UCSF Center for Maternal-Fetal Precision Medicine and the Program on Bioethics. We submit these comments to communicate our support of the recent proposal by the NIH to amend the 'Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules' in order to streamline oversight for human gene transfer research. The 2014 Institute of Medicine report[1] that informed these proposed amendments concluded that much of the science of gene transfer research has advanced significantly and is no longer novel or requiring special/public oversight by the RAC. The current guidelines are a remnant of an earlier era and create unnecessary burdens and complicated reporting practices. We believe the proposed amendments will increase clinical trials in this important area without sacrificing quality, safety, or appropriate oversight. We agree that the vast majority of somatic gene transfer research and gene therapy trials do not require additional review by the RAC and they need not be treated as an exceptional category of research. We are writing to express our support for revising the guidelines and note that in utero gene therapy (IUGT) is likely to emerge as an important clinical modality in treating genetic disorders that can be diagnosed prenatally. We urge you to include specific consideration of this area as you refine and implement changes to the guidelines.

We at the UCSF Center for Maternal-Fetal Precision Medicine are conducting translational and clinical research on fetal therapy for different rare genetic disorders. Our team of clinicians, researchers, bioethicists, and patient advisors is conducting the first FDA approved phase I clinical trial of an in utero stem cell transplantation protocol for fetal alpha thalassemia major. We are also members of the International Fetal Transplantation and Immunology Society (IFETIS), a group of scientists and clinicians focused on developing safe and effective prenatal therapies. In utero gene therapy offers numerous potential advantages over postnatal treatments as outlined extensively in the field.[2] The unique immunological state of the fetus allows the ability to induce tolerance to missing proteins, thus circumventing one of the most important issues with postnatal replacement. There may be additional benefits in being able to treat neurological diseases before the blood brain barrier forms. Finally, in utero therapy may be

effective in treating severe diseases that cause in utero or early postnatal demise, or progressive organ damage that begins in utero.

We believe that there are important criteria that should be carefully assessed when evaluating in utero gene therapy trials. Some of the criteria that have been raised in discussions include the needs for:

1. Accurate prenatal diagnosis with a good understanding of the genotype/phenotype correlation affecting clinical prognosis.
2. Maternal safety: While preclinical studies of IUGT have not demonstrated safety concerns for mothers, an assessment of maternal exposure should be a part of clinical IUGT programs.
3. Fetal safety: One of the goals of prenatal therapy is to induce tolerance to the missing protein and clinical efforts should specifically measure this response, when relevant. Notably, tolerance to the viral vector has not been seen in preclinical studies. Germline integration has also not been observed in preclinical studies but must be included in the clinical assessment when possible.
4. Assessment of ethical issues around potential coercion, non-directive counseling, and partial treatment of a fatal disease
5. Involvement of multidisciplinary teams with specific local expertise in fetal surgery/therapy, genetics, and bioethics.
6. Robust community engagement programs with potential participants in order to integrate participant perspectives throughout the research process.

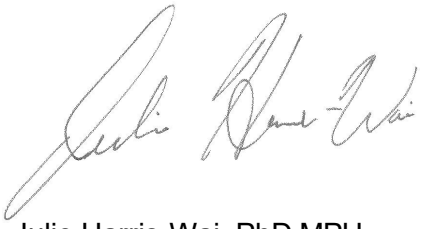
Pregnant women are underrepresented in all clinical trials for a variety of reasons, including increased regulatory scrutiny. Efforts to protect these vulnerable populations have resulted in knowledge gaps for providers regarding appropriate management of these patients, with pharmaceuticals being a prime example. While we agree that we need specific risk/benefit assessments and considerations when conducting research during pregnancy, these mechanisms must be streamlined and simplified to incentivize greater research during the prenatal period. Without this important research, we are missing out on a vital opportunity to enhance the health and safety of pregnant women, and their offspring.

Given the complexity of IUGT research, it is essential to have multiple types of expertise on the team, informing and participating in all aspects of the project. This research (like all innovative research) requires careful consideration of the clinical, ethical, scientific, psychosocial, and societal implications throughout the design and implementation. The institutional or external review process is important but cannot replace the role of ethics expertise and patient/participant involvement on the team itself.

Finally, we support the language in the amendment, modifying the roles of institutional biosafety committees (IBCs) to ensure that they are responsible for reviewing human gene trials. We request additional clarification on how institutions will ensure that the IBCs have the appropriate scientific and ethical expertise necessary for providing comprehensive oversight of all gene therapy trials. We believe the RAC should still serve an important role in training and educating iBCs and IRBs to ensure consistency across institutions.

Sincerely,

Tippi MacKenzie, MD
Professor of Surgery
tippi.mackenzie@ucsf.edu



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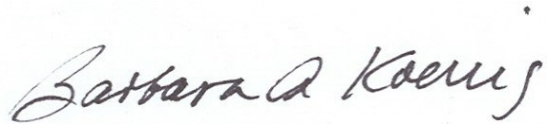

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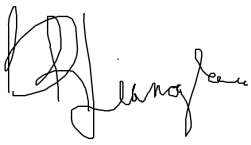

Billie Lianoglou, MS, LCGC
Genetic Counselor, Fetal Treatment Center
Billie.Lianoglou@ucsf.edu

Cited References

1. Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee. Committee on the Independent Review and Assessment of the Activities of the NIH Recombinant DNA Advisory Committee, Board on Health Sciences Policy, Institute of Medicine; Lenzi RN, Altevogt BM, Gostin LO, editors. Washington (DC): National Academies Press (US); 2014 Mar 27.

2. MacKenzie Tippi C. Future AAVenues for In Utero Gene Therapy. Cell Stem Cell. 2018 Sep 6;23(3):320-321.

Submission #95

Name:	Andrea N Ladd
Organization:	University of Wisconsin-Madison
Email:	
Comment:	I applaud the NIH for attempting to reduce the administrative burden of human gene transfer studies. I agree that there is no need for the IBC to duplicate the efforts of the IRB, or for the NIH to duplicate the efforts of the FDA. Removing the IBC review of informed consent documents and NIH registration of HGT trials reduces the time and paperwork for these studies without an obvious loss of safety or oversight. It should be noted that institutions may have to amend their IBC registration processes to capture information about HGT trials that previously relied on Appendix M documents, though the extent of the new burden that this will create will vary widely. I am disquieted, however, by the removal of RAC review in its entirety from the NIH Guidelines. I cannot speak to the usefulness of RAC review for HGT trials specifically, but the consultation of outside experts is in my mind an important element of the Guidelines. It provides a check and balance for high risk work in an ever-evolving scientific and social environment. As currently proposed, there is nowhere in the Guidelines where the NIH is obligated to consult with any external party. Decisions about Major Actions now lie in the hands of a single individual (the NIH Director), whose only external input would now be public comments from the Federal Register, though current language leaves it to the discretion of the director whether such comments will be solicited at all. What will protect scientific decisions from the influences of politics and personal bias? Refocusing the RAC on emerging technologies makes it more applicable to the NIH Guidelines, not less. I urge the NIH to keep RAC review as an integral part of the NIH Guidelines. Andrea N. Ladd, Ph.D. Biological Safety Officer University of Wisconsin-Madison

Submission #96

Name:	
Email:	
Comment:	I oppose the changes proposed to the NIH Guidelines, in particular removing all roles and responsibilities associated with the RAC. If followed through, it will end the most prominent forum for the public discussion of recombinant DNA technology we have had over the last 40 years. Despite such a seminal moment, the accompanying publication by the NIH Director and the FDA commissioner only discuss the elimination of RAC review and reporting of human gene therapy protocols. Even the listing in the federal register is laughably disingenuous: "the NIH proposes to modify the roles and responsibilities of the Recombinant DNA Advisory Committee (RAC)". If the NIH was in fact confident that this was the best possible course of action, why not state directly what the intention is: "the NIH proposes to eliminate all roles and responsibilities of the RAC". Leaving aside the arguments for and against continuing RAC review of human gene therapy, which have been ongoing for more than two decades, Collins and Gottlieb declare that "We have an opportunity to return the RAC to the spirit in which it was founded". While I applaud the sentiment, it is unclear how eliminating all reference to the RAC in the NIH guidelines is consistent with such as a statement. Let us be very clear: the NIH guidelines were written by the RAC, and for almost a decade the RAC was responsible for their constant revision. In early publications, they are referred to as "the RAC's guidelines for recombinant DNA research". To return to the spirit in which the RAC was founded would mean returning control of the process of revision and amendment of the guidelines to the independent experts who comprise this panel, rather than a limited set of government employees (no matter how well intentioned they are). The greatest strength of the RAC has been the public platform it provides for controversial issues surrounding recombinant DNA and biotechnology. With the proposed changes, this transparency is lost and the NIH will be free to execute any Major Action without any prior notice. While gene therapy has dominated the attention of most, other Major Actions of substantial public interest include making pathogenic bacteria resistant to the antibiotics used to treat them, making viruses or bacteria resistant to the vaccines used to protect against them, reducing the containment conditions for handling pathogenic organisms, and even exempting entire classes of research from the NIH guidelines completely. It would seem clear that there is substantial public benefit to keeping review of these actions transparent. While the current NIH director may have the best of intentions, it is critical to keep in mind that the NIH Director is a political appointee, subject to replacement as political administrations change. Without the public nature of RAC review, one might imagine that any of these major actions could be made for purely political reasons. For

example, to punish institutions or individuals who are critical of a political administration and specialize in a certain type of research, or to reward others. Unlike all other federal regulations which must undergo a lengthy process to revise, the NIH guidelines were designed to be revised quickly as needs evolved. In this light, it would seem more prudent to require RAC approval of Major Actions, rather than merely advise, as a hedge against possible political interference in the regulation of recombinant

It is worth noting that this is not the first time the NIH has attempted to eliminate the RAC. In 1996, then director Harold Varus proposed replacing the RAC with a smaller committee to be entitled the Office of Recombinant DNA Activities Advisory Committee (OAC). Similar to the currently proposed changes, this leaner version would no longer review gene therapy protocols, but would continue with the RAC's other responsibilities including administering and proposing modification and amendments to the NIH guidelines. The feedback received was sufficiently negative as to cause the NIH to abandon this strategy and preserve the RAC "because of the historical importance of the RAC as a public platform for discussion of the science…". However, whereas the proposed OAC "would preserve continued public accountability for recombinant DNA research", the current NIH proposal eliminates this

As to human gene therapy, the argument was made that this now "mature" field should not be treated differently from drug or vaccine development. While I dispute the assessment that a few FDA-approved products constitutes a mature field, the point I would like to make is entirely different. Rather than having gene therapy protocols disappear into the sphere of complete confidentiality (certainly in the best interests of industry), instead why not work to bring aspects of drug and vaccine research into the light, particularly in regards to safety data (more in line with public interest). There is no doubt this can be done in a way that

I-A-1-a: On the surface, the change here in consistent with other IBC actions, which are to approve prior to the initiation of work. However, in practice this is unlikely to be the outcome. During my time as chair of an IBC, it was common to have protocols that required both IACUC and IBC approval. In these cases IACUC would commonly withhold approval until the IBC had discussed and approved the protocol as well. With the higher stakes involved in HGT, it would seem very likely that IRBs (who are now used to having the outcomes of an IBC review available as part of their deliberation) will make the same decision. This is in fact logical, as it does not seem possible to separate the biosafety concerns and mitigation strategies noted by the IBC from the information provided on informed consent documents and other ethical aspects of IRB review. Thus, this change is only likely to create confusion and frustration amongst

researchers who feel that IRB approval can and should precede IBC

I-E-4: The definition of RAC should remain, even if other changes are carried through, as it is still referred to under Appendix (D) under past major actions. However, I oppose the complete elimination of the RAC from the NIH guidelines. No justification is provided for the RAC's elimination, as all arguments stated by the NIH Director relate only to

III, III-A, III-A-1-a: No justification is given for removing the RAC's role in category (i), regarding experiments regulated under Section III-A. There is still substantial public interest and benefit in expert deliberation. As an example, the last time the RAC considered an experiment under
-
Director NOT to proceed with approval (in a unanimous 11-0 vote), feeling the potential hazards of introducing the described gene did not outweigh the potential benefits. That discussion is now part of the public record and can be reviewed by anyone with an internet connection in a matter of minutes. Under the proposed change, the NIH Director can approve the experiment with no record of any discussion, or justification of how a decision was reached. This is not in the public interest and again, no justification was provided as to why this change should be

III-C: I agree that FDA needs to take the lead on regulating HGT, and that some redundancy can be eliminated in this process. I disagree that we are sufficiently informed of all the hazards that can befall HGT because a handful of trials have bene completed. Given the diverse array of delivery systems in development, this is premature.
III-D-7-b: No rationale is provided for why the RAC should no longer be available to provide consultation in regards to the biocontainment of highly pathogenic influenza viruses. This would seem to be an appropriate use of a panel of experts, and in line with the concept of bringing the RAC back to its roots.
III-D-7-d: RAC review of major actions, including those involving highly pathogenic influenza viruses should continue. No rationale is provided for deleting this section and there is a strong public interest in preserving this check on NIH authority as well as on public deliberation of such a controversial topic.
III-F-6: No rationale was provided for why the RAC should not be involved in establishing and updating lists of natural exchangers. This is certainly one of the initial missions of the RAC, and with the dramatic influx of metagenomics data it would seem important to continue to involve leading experts in this process.
III-F-8: No rationale was provided for why the NIH Director should no longer seek the advice of the RAC when considering when a recombinant DNA manipulation does not present a significant risk to health of the environment. After more than 40 years of experience with recombinant DNA, one thing that has emerged clearly (as articulated by David Baltimore during the NIH sponsored workshop on the NIH Guidelines in 2017), is that many types of recombinant DNA manipulations that have fallen under the NIH guidelines probably do not need to. Without the

RAC, the only possible choices are to leave the NIH guidelines as they are, frozen in time, or begin exempting new organisms/experiments with no public deliberation. Neither option is acceptable. The public benefit of discussing why classes of research should be exempt, based on decades

IV-C-1: NIH Director should continue to have responsibilities regarding seeking advice from the RAC. Though the current director may have specific plans for a "new" version of the RAC outside the scope of the NIH guidelines, without a mandate here any future director can allow the RAC charter to expire. No rationale was provided for why such a hazard should be ventured with no clear benefit. Even if the RAC is to begin giving advice on subjects beyond recombinant DNA, that would not

IV-C-1-b-(1)-This is probably the most important change to the guidelines that was not discussed in the editorial provided by the NIH Director, and in short this is absolutely shocking. Absolutely no rationale was provided as to the public benefit of eliminating public discussion and expert advice concerning Major Actions. Those in positions of authority at NIH may have the best of intentions, but this represents a substantial consolidation of power that can be abused in the future. The RAC is absolutely essential as a check on government power, as the deterrent involved in passing Major Actions though the court of public deliberation is substantial. As it stands now, only those Actions the NIH (or others) are willing to defend publically are put forth now. With these changes, a

IV-C-1-b-(2)- Again, another historical function of the RAC that is being eliminated with no rationale or benefit provided. Why is it in the public interest for the NIH Director or OSP to receive less advice from a panel of experts when it comes to biosafety and biocontainment? That is the original function of the RAC. Why not restore and expand it, if the RAC is

IV-C-2 and IV-C-2-a: No rationale is provided for why the RAC is being removed from the NIH guidelines. All arguments presented in the NIH Director's editorial can be achieved through modifications to III-C and appendix M, along with IV-C-2-b, -c, -d here. If the RAC is to have a useful role, it must have clearly defined responsibilities in the NIH Guidelines. The NIH Guidelines were written by the RAC and entrusted to the NIH Director for enforcement. This change is a complete betrayal of the trust given by the scientists who more than 40 years ago proclaimed that whether and how to use new biotechnologies is a subject that must be deliberated publically, with input from all interested parties BEFORE a

V-A, No rationale is provided for why the advice of the RAC is no longer necessary for the classification of Risk Groups. With the current deluge of metagenomics sequence data and genome sequence data, the number of

	new organisms being used in laboratory research is rapidly expanding. V-B: Again, why would it be necessary to disallow NIH OSP to request Appendix A: No rationale or public benefit is described for why the NIH Director should not receive advice from experts when classifying microbiological agents. It is unlikely that NIH administrators will have internal access to this type of specialized knowledge as compared with Appendix B: No change is marked in the introductory paragraph. However, if all changes are carried through, the following statement will not make sense: "A special committee of the American Society for Microbiology will conduct an annual review of this appendix and its recommendation for changes will be presented to the Recombinant DNA Advisory Committee as proposed amendments to the NIH Guidelines." I love this sentence, and think it is a great idea. However, if the RAC is to survive in the NIH guidelines, it should be because the NIH Director favors public deliberation of biotechnology as well as a check on government authority, not because one or two references escaped the Appendix C- No changes were noted in this section, which is nice because Appendix C-IX-A: No rationale or public benefit is described for why the NIH Director should not receive advice from experts when classifying risk groups. It is unlikely that NIH administrators will have this type of Appendix D: The change "Entries up to and including D-118 were approved using a process that involved the RAC" does not make sense if the RAC is removed from the definition list and from throughout the Appendix I-II-A and I-II-B-2: No rationale or public benefit is described as to why the RAC should not be consulted on the certification of new host-vector systems. While very few such requests are likely received by NIH, this is likely driven by the association of the RAC with HGT over the past few decades. My experience on the IBC has been that there remain many commonly used systems that should be going through this process, but haven't. This is an area where the NIH guidelines need to evolve and be more proactive.

Submission #

Name:	
Email:	
Comment:	Regarding Deletion of Appendix M: Complete removal of the RAC component to HGT review will place even more significance on local oversight. It seems then that since IBC review will carry more weight, the NIH should provide more guidance on how an IBC should carry out a risk assessment, not less. Deleting Appendix M results in less guidance. Further, if part of the justification for changing the NIH Guidelines is strengthened oversight at the local level, deleting Appendix M has the potential undermine that strength as IBC's struggle to define the proper criteria by which to review HGT studies. For these reasons, I feel the NIH Guidelines should retain the "Points to Consider" for risk assessment of HGT research. In addition, if the NIH really wants to streamline the HGT oversight process, it should start by establishing containment criteria for a hospital/clinical setting (e.g., a "Clinical Safety Level"). Applying NIH physical containment criteria to a hospital/clinical setting does not make sense and often leads to confusion. Biosafety Level criteria, as written, are sometimes at odds with Infection Control and Pharmacy/Hazardous Drug Safety guidelines and standards. The NIH should engage with APIC/HICPAC/CDC or Pharmacy professional groups to work towards reconciling these.

Submission #

Name:	Betsy Foss-Campbell
Organization:	American Society of Gene & Cell Therapy
Email:	bfoss@asgct.org
Comment:	Please see attachment.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	- - comment-form/uploads/ASGCT Comments on Proposed Amendments to the NIH Guidelines for RAC, Final.pdf

AMERICAN SOCIETY of GENE & CELL THERAPY

Jessica Tucker, PhD
Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892-7985

Re: Proposal to Amend *NIH Gu del nes* related to oversight of human gene transfer clinical research protocols

Dear Dr. Tucker,

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to provide comments on the National Institutes of Health (NIH) proposal to amend the *NIH Gu del nes for Research Involv ng Recomb nant or Synthet c Nucle c Ac d Molecules (NIH Gu del nes)*. ASGCT is the premier membership organization consisting of scientists, physicians, and other professionals involved in gene and cell therapy. The Society's mission is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease.

ASGCT supports the NIH proposal to eliminate Recombinant DNA Advisory Committee (RAC) review and reporting requirements for human gene transfer protocols. ASGCT also supports the related NIH proposal to modify the roles of Institutional Biosafety Committees in reviewing human gene transfer to be consistent with review of other covered research. ASGCT holds these positions for the reasons outlined below.

Elimin ting del ys in the delivery of new tre tments

The substantial duplication in the submission of initial protocols, annual reports, amendments, and reports of serious adverse events may cause unnecessary delays in the approvals of gene therapies, some of which have the potential to affect survival of patients with serious, potentially fatal diseases. Months of staff time is typically required for the preparation of distinct documents for FDA and RAC protocol review, by research, development, manufacturing, clinical affairs, regulatory, quality control, quality assurance, project management, and other departments.[i] In addition, the RAC meets only approximately four times a year,[ii] so approvals of gene therapies that currently require RAC review must await the next available review date.

S fety concerns will continue to be ddressed

While ASGCT acknowledges that safety concerns remain for gene therapy research, scientific progress in the field has reduced the need for additional monitoring by the RAC. Since the time when the RAC's mission was expanded to include the review and discussion of human gene therapy protocols, significant scientific advancements—including in safety precautions and gene-transfer efficiency and delivery—have answered many of the questions regarding safety and efficacy that were unanswered in the 1990s. ASGCT agrees

555 East Wells Street, Suite 1100 • Milwaukee, WI 53202-3823 • (414) 278-1341 • Fax (414) 276-3349 • www.asgct.org • info@asgct.org

with the position of the FDA and NIH that there is no longer sufficient evidence to support that the risks of gene therapy are entirely unique and unpredictable, and thus the field no longer requires special oversight that falls outside the existing framework for other areas of biomedical research for ensuring safety.[iii]

In addition to scientific progress in the field, the FDA framework for oversight of medical product safety has advanced to robustly address safety issues across most areas of biotechnology research. FDA is now staffed by professional reviewers in the CBER Office of Tissues and Advanced Therapies (OTAT) whose expertise in the areas of cell and gene therapy, and whose knowledge of drug development, is broad and deep.[iv] As a result, changes have been initiated over time to decrease RAC oversight. NIH and FDA agreed in 1995 that NIH would limit its public reviews to novel protocols, while FDA would assume primary responsibility for reviewing gene therapy protocols.[iv] The 2014 Institute of Medicine report and recommendations, implemented in 2016, further limited RAC review to gene therapy protocols that raised exceptional issues or concerns. Only three of 275 such protocols since that change went into effect have warranted RAC review.[iii] For these reasons, ASGCT has expressed previous support of eliminating RAC review of gene therapy protocols[i] and views the current proposal to do so as the next step in removing remaining duplication in the process of gene therapy protocol review.

Under the NIH proposal, OTAT would continue to provide review of gene therapy protocols. Additional assessment of gene therapy protocols and review of their safety information would also continue to be provided by Institutional Biosafety Committees (IBCs), which have local oversight for research, as is the case for other areas of biomedical research. ASGCT finds that the expectations of IBCs in light of the proposed changes have been articulated clearly in the proposed revisions to the *NIH Gu del nes*.

Public tr nsp rency

Implementation of other means of informing the public has occurred since the establishment of the RAC in 1974 that provide public transparency regarding gene therapy research, such as the institution of ClinicalTrials.gov. Moreover, the RAC would not be eliminated under the proposal, but its purpose would return to its original intended purpose of advising the NIH director on the scientific, safety, and ethical issues associated with emerging biotechnology. With the emergence of new biotechnologies beyond the realm of recombinant DNA, the RAC would better fulfill its purpose by serving as an advisory board on current and future emerging technologies. ASGCT acknowledges the benefits of continuation of this role for the RAC, as well as the past contributions of the RAC in advancing the science of gene therapy.

ASGCT thanks the NIH for its consideration of these comments. Please let us know if you have any questions.

Sincerely,

Michele P. Calos, PhD
ASGCT President

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[i] McGarrity, G. M. (2012). It's time to end RAC review of gene therapy protocols. *Molecular Therapy* 20(6): 1079-1080.
[ii] Department of Health and Human Services. (2017). Charter: Recombinant DNA Advisory Committee. Accessed on 10/14/18 at https://osp.od.nih.gov/wp-content/uploads/RAC_Charter_2017_508.pdf.
[iii] Collins, F. S. and Gottlieb, S. (*2018). The next phase of human gene-therapy oversight. *N Engl J Med* 379: 1393-1395.
[iv] Institute of Medicine. (2014). Oversight and review of clinical gene transfer protocols: Assessing the role of the Recombinant DNA Advisory Committee. Washington, D. C.: The National Academies Press.

Submission #30

Name:	
Email:	
Comment (limit: 15,000 characters):	Jessica Tucker, Ph.D. 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) – Request for Comments Dear Dr. Tucker: Thank you for providing the research community with an opportunity to submit comments, as published in the Federal Register (FR) on August 17, 2018 on the proposed changes to NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines.) I am writing on behalf of Partners HealthCare System, which includes the Brigham and Women's Hospital (Brigham), Massachusetts General Hospital (MGH), and McLean Hospital. All three hospitals are principal teaching affiliates of Harvard Medical School, each with a substantial portfolio of federally-funded research that includes animal activities. In FY18 Partners HealthCare received $1.7 billion in research funding from federal and non-federal sources. Additionally, the Partners HealthCare Institutional Biosafety Committee (IBC) has reviewed and approved over 136 clinical trials since 2011 and is currently monitoring 76 active trials involving the use of recombinant or synthetic nucleic acid molecules. We endorse the proposed changes to the NIH Guidelines. Reducing the regulatory burden on Principal Investigators and their clinical trials that use well-established products and technologies of recombinant and synthetic nucleic acid molecules will help accelerate the initiation of clinical trials and ensure compliance with existing regulations. While we generally agree with the proposed changes to Section III-C and the removal of Appendix L and Appendix M, and endorse these changes that removes Recombinant Advisory Committee (RAC) oversight of Human Gene Therapy (HGT) and HGT protocol reporting requirements to the Office of Science

Policy (OSP), we do have several concerns and comments regarding these changes. First, we would appreciate clarification on the OSP view of the new role for the IBC in human subject research involving recombinant or synthetic nucleic acid molecules. Second, we would appreciate formal guidance on IBC communication with federal agencies and other Institutions. Third, we would appreciate a clearer understanding the new role of the RAC and the NIH Guidelines with these changes. The RAC provides OSP and the NIH Director with valuable advice on current risks and trends in biological research and this expertise

The biomedical and life sciences have advanced significantly since the NIH Guidelines were first published. HGT experiments have matured to the point that it makes sense to review the oversight process, but we argue that other areas have also reach a level of maturity that would benefit from a similar review (e.g., as animal experiments and viral vector usage.) And though the NIH Guidelines have been revised multiple times, they do not address current trends and new risks posed to Institutional Biosafety Committees. Synthetic biology, CRISP-Cas9 technology, and gene drive experiments are areas that

* The OSP should perform a similar review of mature technologies covered under Section III-D and III-E of the NIH

* The NIH Director should update the RAC charter to ascertain current and future risks of leading-edge biological research and

With OSP no longer providing oversight at the federal level, IBCs are left without a federal point of contact to voice concerns identified during risk assessments. Appendix M provides clear guidelines for federal communication and risk assessments which would be lost. This potentially leaves IBCs disconnected from other IBCs and federal agencies in reporting identified risks and learning from other Institution’s risk assessments. In

previous reviews of the clinical study. This is especially true in situations where an IBC declined to host a trial over of biosafety concerns as this may not be recorded in public IBC minutes, but would also include sharing best practices and mitigation

* Add language to the NIH Guidelines that requires sponsors of multisite human subject research trials to provide new sites a

	list of all sites that the trial was submitted to and previous IBC The current changes are stated to align the review of recombinant and synthetic nucleic acid molecule research in humans with the current review of laboratory research. However, it is not clear what the OSP expects IBCs to review in a HGT trial. Current guidance for reviews found in Appendix M is being removed and supplemental guidance provided with the announcement suggest only reviewing shedding and administration. We would benefit from a clearer understanding include the aspects of the biological agent to review, what portion or the trial to review, containment levels, and what, if any, follow up review should be performed. The changes seem to imply that IBCs should no longer consider the risks of the biological agent itself (i.e. potential reversion to competent viral vector replication) or adverse events. Additionally, it is unclear what exposures to biological agents should be reported to OSP in the context of a clinical trial. For example, would reportable incidents include potential exposure between human subjects and close contacts? Finally, supplemental guidance with these changes suggests that review should stop at administration despite the potential for risks in biological specimens taken from * The OSP should provide guidance on the Risk Assessment process and containment levels for HGT trials. * The OSP should clarify if adverse events and significant adverse events should be reported to the IBC. * The OSP should clarify if exposure in the clinical setting is reportable. * The OSP should clarify what types of clinical protocol * The OSP should clarify at what point the IBC review of a trial It is our belief that local oversight by Institutional Biosafety research has been effective at ensuring the safety of the community and environment, clinical staff, and human subjects and will continue to do so. Reducing the regulatory burden will contribute to timely transition of gene therapy products into I greatly appreciative the opportunity to provide the OSP with these comments regarding the proposed changes to the NIH Guidelines.

	Yours sincerely, Anne Klibanski, MD Chief Academic Officer Partners HealthCare
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/Partners NIH Comment Letter.pdf

October 16, 2018

HARVARD MEDICAL SCHOOL

Anne Klibanski, M.O.
Chief Academic Officer
Partners Healt/rCare
Laurie Carrol Gutlrnrf *Professor of Medicine*
Dean for Academic Programs lii Partners HealthCare
Harvard Medical SclronT

Jessica Tucker, Ph.D.
Office of Science Policy
ational 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)*- Request for Comments

Dear Dr. Tucker:

Thank you for providing the research community with an opportunity to submit comments, as published in the Federal Register (FR) on August 17, 2018 on the proposed changes to *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines.)* I am writing on behalf of Pa11ners HealthCare System, which includes the Brigham and Women's Hospital (Brigham), Massachusetts General Hospital (MOH), and McLean Hospital. All three hospitals are principal teaching affiliates of Harvard Medical School, each with a substantial portfolio of federally-funded research that includes animal activities. In FY18 Partners HealthCare received **$1**.7 billion in research funding from federal and non-federal sources. Additionally, the Pm1ners HealthCare Institutional Biosafety Committee (IBC) has reviewed and approved over 136 clinical trials since 2011 and is currently monitoring 76 active trials involving the use of recombinant or synthetic nucleic acid molecules.

We endorse the proposed changes to the *NIH Guidelines.* Reducing the regulatory bmden on Principal [nvestigators and their clinical trials that use well-established products and technologies of recombinant and synthetic nucleic acid molecules will help accelerate the initiation of clinical trials and ensure compliance with existing regulations.

While we generally agree with the proposed changes to Section III-C and the removal of Appendix Land Appendix M, and endorse these changes that removes Recombinant Advisory Committee (RAC) oversight of Human Gene Therapy (HGT) and HGT protocol reporting requirements to the Office of Science Policy (OSP), we do have several concerns and comments regarding these changes. First, we would appreciate clarification on the OSP view of the new role for the IBC in human subject research involving recombinant or synthetic nucleic acid molecules. Second, we would appreciate formal guidance on IBC communication with federal agencies and other Institutions. Third, we would appreciate a clearer understanding the new role of the RAC and the NIH Guidelines with these chm1ges. The RAC provides OSP and the NIH Director with valuable advice on current risks and trends in biological research and this expe11ise should be retained.

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The biomedical and life sciences have advanced significantly since the *NIH Guidelines* were first published. HGT experiments have matured to the point that it makes sense to review the oversight process, but we argue that other areas have also reach a level of maturity that would benefit from a similar review *(e.g.,* as animal experiments and viral vector usage.) And though the *NIH Guidelines* have been revised multiple times, they do not address current trends and new risks posed to Institutional Biosafety Committees. Synthetic biology, CRISP-Cas9 technology, and gene drive experiments are areas that would benefit from guidance from the OSP and the RAC.

Recommendations:

- The OSP should perform a similar review of mature technologies covered under Section III-D and III-E of the *NIH Guidelines.*
- The NIH Director should update the RAC charter to ascertain current and future risks of leading-edge biological research and provide OSP guidance in those areas.

With OSP no longer providing oversight at the federal level, IBCs are left without a federal point of contact to voice concerns identified during risk assessments. Appendix M provides clear guidelines for federal communication and risk assessments which would be lost. This potentially leaves IBCs disconnected from other IBCs and federal agencies in reporting identified risks and learning from other Institution's risk assessments. In multisite trials, it would be useful for an IBC to have access to previous reviews of the clinical study. This is especially true in situations where an IBC declined to host a trial over of biosafety concerns as this may not be recorded in public IBC minutes, but would also include sharing best practices and mitigation strategies for the trial.

Recommendations:

- Add language to the NIH Guidelines that requires sponsors of multisite human subject research trials to provide new sites a list of all sites that the trial was submitted to and previous IBC approval letters.

The current changes are stated to align the review of recombinant and synthetic nucleic acid molecule research in humans with the current review of laboratory research. However, it is not clear what the OSP expects IBCs to review in a HGT trial. Current guidance for reviews found in Appendix M is being removed and supplemental guidance provided with the announcement suggest only reviewing shedding and administration. We would benefit from a clearer understanding of what a new HGT risk assessment would entail. This should include the aspects of the biological agent to review, what portion or the trial to review, containment levels, and what, if any, follow up review should be performed. The changes seem to imply that IBCs should no longer consider the risks of the biological agent itself (i.e. potential reversion to competent viral vector replication) or adverse events. Additionally, it is unclear what exposures to biological agents should be reported to OSP in the context of a clinical trial. For example, would reportable incidents include potential exposure between human subjects and close contacts? Finally, supplemental guidance with these changes suggests that review should stop at administration despite the potential for risks in biological specimens taken from subjects after the final administration.

Recommendations:

- The OSP should provide guidance on the Risk Assessment process and containment levels for HGT trials.
- The OSP should clarify if adverse events and significant adverse events should be reported to the IBC.
- The OSP should clarify if exposure in the clinical setting is reportable.
- The OSP should clarify what types of clinical protocol amendments should be submitted to the IBC.
- The OSP should clarify at what point the IBC review of a trial is complete.

It is our belief that local oversight by Institutional Biosafety Committees and Institutional Review Boards of biomedical research has been effective at ensuring the safety of the community and environment, clinical staff, and human subjects and will continue to do so. Reducing the regulatory burden will contribute to timely transition of gene therapy products into clinical trials.

I greatly appreciative the opportunity to provide the OSP with these comments regarding the proposed changes to the NIH Guidelines.

Yours sincerely,

Anne Klibanski, MD
Chief Academic Officer

Submission #31

Name:	Darby Hull
Organization:	
Email:	Dhull@primr.org
Comment (limit: 15,000 characters):	Please see attached.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/PRIMR_comments_Oct16.pdf

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

October 16, 2018

Submitted electronically at https://osp.od.nih.gov/comment-form-nih-guidelines/

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

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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**

[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.

Submission #32

Email:	stephanie.pyle@advarra.com
Comment (limit: 15,000 characters):	Dear Director, The proposed changes to the NIH Guidelines are positive and will streamline the IBC review process for review of human gene transfer (HGT) studies. The requirements to register studies with NIH OSP as required under Appendix M-I-A and M-I-B complicated and delayed the process of obtaining IRB and IBC approval for HGT studies. The reporting requirements in Appendix M-I-C were largely duplicative given the roles of the FDA, the IRB, and the IBC. We applaud the NIH for proposing to eliminate these requirements. However, completely deleting Appendix M might have detrimental effects. The removal of Appendix M will leave IBCs with a lack of guidance regarding how to perform reviews for HGT studies. Without the guidance provided by Appendix M, IBCs may be unclear about their jurisdiction within the clinical setting, as most IBCs are focused on the laboratory environment and vivaria. It would be beneficial if NIH Guidelines explicitly stated the scope and duration of the IBC's responsibilities for HGT studies within the clinical setting. If the investigational product containing recombinant or synthetic nucleic acids is manufactured offsite, does the IBC's jurisdiction begin at the institution performing the clinical research when the investigational product arrives onsite? Additionally, many IBCs relied on the documents list from Appendix M-I-A as the baseline documents to request for review of HGT studies. Without the documents listed in Appendix M-I-A, IBCs may: • Conduct reviews without sufficient documentation, • Compromise the quality of IBC review because of the absence of a regulatory foundation to require documentation, and • Be unaware of what documents to request for review of HGT studies without a regulatory driver. While the documents list from NIH Guidelines Appendix M-I-A is useful, we suggest replacing the Description of the Product (Appendix M-I-A-4 a-f) with Appendix M-I-A-4 a, b and f, which ask for a description of: a) The vector (including methods of attenuation), b) The transgene (including regulatory sequences), and f) The gene transfer delivery method. This information is vital to the risk assessment process for the recombinant or synthetic nucleic acids and should not pose a burden to study personnel soliciting IBC approval, as it is typically included in the study protocol or investigator's brochure. The remaining questions Appendix M-I-A-4 c-e

	deal with manufacturing issues that are addressed during the FDA's IND review process and should be excluded from IBC review at the institution performing the research. Lastly, the functions of the IBC as they pertain to requesting RAC review as specified in Section IV-B-2-b-(1) should be revised to remove the requirements associated with registration of HGT studies but should continue to allow the IBC to request RAC review of novel uses of recombinant or synthetic nucleic acid molecules for which the risks may be difficult to assess or may pose significant scientific, societal, or ethical Thank you for your support of scientific research and the opportunity to Kind regards, Daniel Eisenman, PhD, RBP, SM(NRCM), CBSP Director, Biosafety
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	form/uploads/Advarra_Comments_on_Proposed_NIH_Guidelines_Vfinal.pd

October 16, 2018

Office of Science Policy, National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

RE: 83 FR 41082 "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)"

Dear Director,

The proposed changes to the NIH Guidelines are positive and will streamline the IBC review process for review of human gene transfer (HGT) studies. The requirements to register studies with NIH OSP as required under Appendix M-I-A and M-I-B complicated and delayed the process of obtaining IRB and IBC approval for HGT studies. The reporting requirements in Appendix M-I-C were largely duplicative given the roles of the FDA, the IRB, and the IBC. We applaud the NIH for proposing to eliminate these requirements. However, completely deleting Appendix M might have detrimental effects.

The removal of Appendix M will leave IBCs with a lack of guidance regarding how to perform reviews for HGT studies. Without the guidance provided by Appendix M, IBCs may be unclear about their jurisdiction within the clinical setting, as most IBCs are focused on the laboratory environment and vivaria.

It would be beneficial if NIH Guidelines explicitly stated the scope and duration of the IBC's responsibilities for HGT studies within the clinical setting. If the investigational product containing recombinant or synthetic nucleic acids is manufactured offsite, does the IBC's jurisdiction begin at the institution performing the clinical research when the investigational product arrives onsite?

Additionally, many IBCs relied on the documents list from Appendix M-I-A as the baseline documents to request for review of HGT studies. Without the documents listed in Appendix M-I-A, IBCs may:

- Conduct reviews without sufficient documentation,
- Compromise the quality of IBC review because of the absence of a regulatory foundation to require documentation, and
- Be unaware of what documents to request for review of HGT studies without a regulatory driver.

While the documents list from NIH Guidelines Appendix M-I-A is useful, we suggest replacing the Description of the Product (Appendix M-I-A-4 a-f) with Appendix M-I-A-4 a, b and f, which ask for a description of:

a) The vector (including methods of attenuation),
b) The transgene (including regulatory sequences), and
f) The gene transfer delivery method.

This information is vital to the risk assessment process for the recombinant or synthetic nucleic acids and should not pose a burden to study personnel soliciting IBC approval, as it is typically included in the study protocol or investigator's brochure. The remaining questions Appendix M-I-A-4 c-e deal with manufacturing issues that are addressed during the FDA's IND review process and should be excluded from IBC review at the institution performing the research.

Lastly, the functions of the IBC as they pertain to requesting RAC review as specified in Section IV-B-2-b-(1) should be revised to remove the requirements associated with registration of HGT studies but should continue to allow the IBC to request RAC review of novel uses of recombinant or synthetic nucleic acid molecules for which the risks may be difficult to assess or may pose significant scientific, societal, or ethical concerns.

Thank you for your support of scientific research and the opportunity to comment on the proposed revisions to NIH Guidelines.

Kind regards,

Daniel Eisenman, PhD, RBP, SM(NRCM), CBSP
Director, Biosafety Services, Advarra

Submission #33

Date	10/17/2018
Name:	Julie Savage
Organization:	ABSA
Email:	julie@absaoffice.org
Comment (limit: 15,000 characters):	Please see attached.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/NIH_Comment_Letter_ABSA_JS.pdf

ABSA INTERNATIONAL
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October 16, 2018

Office of Science Policy, National Institutes of Health
6705 Rockledge Drive, Suite 750
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RE: 83 FR 41082 "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)"

Dear Director,

The American Biological Safety Association (ABSA) International welcomes the opportunity to comment on the "*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)*" published 17 August 2018. ABSA International provides a critical expertise for this topic as many of its members are extensively involved in implementing the *NIH Guidelines* and fulfilling certain roles therein.

There is one overarching and pervasive concern expressed by biosafety professionals:

Concern: Eliminating the Recombinant DNA Advisory Committee (RAC) from performing a transparent and scientific review of Human Gene Transfer (HGT) clinical trials is of great concern and deemed inadvisable. Removing the RAC, a body of world-class experts, from being an integrated and defined component of NIH research oversight for recently emerged and emerging technologies has a negative impact on the safe conduct of research.

Recommendation: Continue RAC review for emerging and recently emerged technologies, for Phase I and first in human use research, for decisions regarding major actions, and for monitoring incident reports. Use this opportunity to detail a process for the NIH Director, and for Institutional Biosafety Committees (IBC) and investigators to solicit input from this committee of world-class experts. Revise the *NIH Guidelines*, the RAC Charter, and other pertinent documents accordingly and release for public review and comment.

Why keep the RAC?

The RAC is a body with technical expertise of a scale and breadth rarely accessible to research entities. While gene therapy, gene transfer, and gene editing technologies have moved from being an emerging technology to emerged in their biotechnology and clinical applications, as specified by the NIH Director and FDA Commissioner, the move to clinical research is recent. The emergence of CRISPR and CAR-T technologies opened the door to a wide variety of clinical applications yet we are still learning more about these technologies and their associated risks. The collective expertise on the RAC was invaluable in the review of novel, complex technologies and would continue to be so in this role, as well as in the continued review of recently emerged technologies. The exercise of RAC member responsibilities itself functions to continuously raise the level of expertise of its members and enables a holistic assessment for the multiple components participating in, or potentially affected by, research.

Transparency in the process for soliciting RAC input, by inclusion in the *NIH Guidelines*, will continue to promote research rigor in study design and safety for all persons involved. The description for the RAC to exist as an advisory body in this subsequent proposed amendment to the *NIH Guidelines* is not sufficiently specific to be informative. It is unclear w
hat the agenda will be for the RAC once it is removed from the *NIH Guidelines*. The plan for removal of the RAC, and for decisions previously made by the RAC to rest with the NIH Director and the Office of Science Policy (OSP), are of great concern particularly with regard to Major Actions (Section III-A-1). Decisions for research involving risk at the level of a Major Action should require expertise and input from the RAC, in a manner transparent to the public and in a procedure consistently applied.

Concerns for the changing role of the RAC regarding adequate review and research oversight persist from the those raised in comment to 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, submitted by ABSA International on November 30, 2015, for what became the April 2016 Amendment. Changes to diminish the role of the RAC made in the 2016 *NIH Guidelines* amendment were substantial, significant, and unfortunately sufficiently recent to preclude an evaluation of the effect of those changes.

Institutional Biosafety Committees

Institutional Biosafety Committees (IBC) are concerned that there is no formal mechanism remaining in the amendment for the IBC to seek guidance from the RAC on specific concerns that arise during the review process. Previously, the referral of protocols for public RAC reviews served this purpose for the numerous institutions whose research calls for registered IBCs. The absence of the RAC's involvement in clinical research oversight is already being observed, restricting access to pertinent expertise not widely available, *prior* to completion of public review and official implementation of the proposed amendment.

Many IBCs, excluding the long-standing academic medical centers traditionally at the forefront of gene therapy, lack the expertise to adequately conduct a risk assessment for clinical research as applied in pharmacy and clinical settings; and conversely, risk assessments and research oversight in clinics and hospitals differ vastly from the application of the *NIH Guidelines* and biosafety principles seen in the conduct of relevant pre-clinical research.

According to the NIH Office of Science Policy (OSP, 26 August 2018), the last 10 years has seen a 59% increase in IBC registrations, which illustrates the rapid growth of this exciting clinical application. The majority of these IBCs are for locations which review HGT clinical research. For many locations, pharmacy and clinical staff have little to no experience in biosafety/biosurety and view the handling of HGT products akin to chemotherapy. The safe conduct of HGT trials requires appropriate risk assessments and significant education, particularly pertaining to the replication competent biologicals being utilized. Research test articles and technologies applied to human subjects retain the risks specific to the material involved, and potential risks are increasingly being reported (e.g., CAR-T cytokine release syndrome, additional CRISPR off-target effects, and significant genomic damage following CRISPR-Cas9 nucleic acid break repair). The expertise of the RAC is clearly needed to provide far-reaching support for the safe research of these emerging and recently emerged technologies.

Justification for Change

Justification for eliminating RAC review is drawn from comparing the oversight of HGT studies to other areas of clinical research; however, not all clinical research studies pose the same types of risk.

Similarly, not all oversight bodies share the same focus on research. All layers of oversight protect different portions of a 360° view of clinical research and each have their importance. Review by one body such as the RAC for ethical, scientific, and risk assessment of HGT research is outside the FDA purview, and would remain beneficial.

Removing redundancy in research protocol processes is a good goal, but should not be done at the expense of reducing safety. Returning the mission of the RAC to its original purpose, belies the progress and refinement of the RAC duties to meet needs later identified. Returning to the past is not preparing for the future.

Decreasing the Research Burden is Supported Overall

Biosafety professionals generally support and embrace the spirit of the proposed amendment to the *NIH Guidelines* to further streamline the processes for research oversight for HGT clinical trials. The efficiencies gained in removing duplicative steps decreases the research burden and may clarify for investigators the focus of oversight bodies involved in reviewing HGT clinical applications. Removing the requirement to complete Appendix M, allows for less redundancy and confusion between the IBC and the IRB. The documents required under Appendix M have been very helpful for IBC review, pulling out information on the study drug, personnel involvement, and trial logistics. Obtaining the pertinent information is still valuable for biosafety review and identification of containment and training needs. Conversion of Appendix M to a guidance document with significant narrowing to highlight the relevant information is encouraged.

Additional Comments

Please review the additional comments provided in the attached Excel table. Observations fall into general comments and those pertinent to specific proposed text. Issues include, but are not limited to: gaps in oversight that arise with the proposed amendment, additional RAC concerns, proposals, and errors/omissions in the proposed text.

ABSA International appreciates the opportunity to review the proposed amendment to the NIH Guidelines. The comments provided are respectfully offered for your consideration.
Please contact me with any questions or to request clarification.

Respectfully,

Patrick Condreay

Patrick Condreay, PhD, RBP
President, ABSA International

ABSA International

Document:	Document Citation/Number: 83 FR 41082
"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)"	https://www.federalregister.gov/documents/2018/08/17/2018-17760/national-institutes-of-health-nih-office-of-science-policy-osp-recombinant-or-synthetic-nucleic-acid
	https://www.gpo.gov/fdsys/pkg/FR-2018-08-17/pdf/2018-17760.pdf

Table 1: General Comments

Observation/Concern	*Comment*	*Proposed change*
There is a gap in oversight of human gene transfer clinical studies under the current proposal.	Registration of Phase 1 studies is not mandatory on ClinicalTrials.gov as these studies do not meet the definition of an applicable clinical trial (ACT) as defined in section 402(j) of the PHS Act. ClinicalTrials.gov does not provide an adequate measure of oversight or transparency as clinical trial registration is not required until 21 days after enrolling the first human subject.	Maintain RAC for review of Phase I trials that meet the current criteria
A loophole exists in oversight of human gene transfer clinical studies under the current proposal.	Under FDAAA 801, the manufacture of a drug, biological, or device product in the US renders the study to be an ACT. A drug or biological product manufactured outside the US could be used and would not fall under FDAAA 801.	Expand scope of FDAAA 801 to include products manufactured outside of the US
Reducing duplications in submissions to the FDA and NIH could be met following a process similar to that in the European Union (EU) where registration of clinical trials are harmonized among multiple interests.	Use of FDA forms for both NIH and FDA purposes. FDAAA801 will need to be updated to reflect any changes to NIH Guidelines	Maintain registering with NIH but allow for the use of FDA forms; expand scope of FDA forms to include risk assessment questions similar to EU registering requirements

ABSA International

Proposed RAC focus to emerging technologies will miss newly identified risks that impact current research	Proposed text shifts the focus of the RAC to emerging biotechnologies only; it is not stated to continue review of current research protocols in the new system. Example concerns: (1) Existing biotechnology (e.g. CRISPR/Cas 9) are now being used in humans without knowledge of off-target impact; (2) Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements (Kosicki, 2018)	Maintain, and potentially increase, RAC focus to continue evaluating risks in research involving existing and emerging biotechnology
Proposed changes may lead to dissolution of the RAC, and remove a national resource for research.	Removal of the RAC from the Guidelines, in conjunction with a 2-year revolving charter may lead to the dissolution of the committee even with its authorization in the Public Health Service Act. RAC charter will need to be updated for revised role and include recommended and responsive changes for continued role in research oversight.	Propose changes to the RAC charter and oversight be made that are responsive to stated concerns; that the NIH Director solicit input from impacted and involved parties; and that the draft charter and oversight be released to the public for review and comment.
What is the mechanism by which the NIH Director can solicit advice from the RAC? What is the mechanism for the IBC?	Inclusion of the process for soliciting input from the RAC on research protocols provide assurance to principal investigators and research entities of review by multiple world-class experts in their field. Transparency in this process for soliciting RAC input will continue to promote research rigor in study design and safety for all persons involved.	Do not eliminate every mention of the RAC from the Guidelines; maintain the RAC for Phase I and first in human research.
There is the potential that not all local IBCs and IRBs have the knowledge to address all the unknowns present.	The rapid growth of research involving nucleic acids and the conduct of human gene transfer studies outpaces the expertise available for service on IBCs. Few, if any, institutions would have IBC members with technical expertise at the level of members of the RAC.	Maintain registration with the NIH for review of projects of recombinant nature to ensure experts in this field have one central clearing house; clinicaltrials.gov is a central database but does not offer the same transparency for IBCs.

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There needs to be an option/requirement for Major Action, including HGT, to ensure applicable research goes back to NIH OSP for RAC review.	The criteria from the 2016 amendment should be added as to when the study would benefit from RAC review.	Include "New technologies; use of new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk; study relies on preclinical safety data that were obtained using a new preclinical model of unknown and unconfirmed value; or the proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate protocol rigorously;" as text to identify research areas subject to RAC review.
Appendix M has aided in assessing biosafety risks, identifying opportunities for mitigation, and determing training needs. Appendix M may serve a useful role even if deleted from the NIH Guidelines.	The IBC will continue to focus on worker safety with removal of Appendix M, and conduct thorough site-specific reviews as conducted for other protocols. The use of Appendix M has provided important details for the risk assessment of clinical research, including the observation that pharmacy and clinical staff have little to no experience on biosafety, disinfection, personal protective equipment, and engineering controls. The significant need for substantial training is commonly observed for the safe conduct of clinical trials.	Propose Appendix M be converted to a guidance document following revision.

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Table 2: Specific Comments				
Section Name or #	***Paragraph or #***	***Text at issue***	***Proposed change***	***Comment***
SUPPLEMENTARY INFORMATION	Paragraph 1	"Oversight mechanisms for ensuring HGT proceeds safely" are stated to "have sufficiently evolved to keep pace with new discoveries in this field." How was the sufficiency determined?	Define and describe "sufficient oversight". Include argument and references to support the characterization as sufficient oversight.	HGT clinical research differs from other clinical research. It is a relatively new field and oversight should continue to have unique mechanisms as clinical research proceeds. There is some precedent as clinical research involving radioactive materials as a research component should include radiation safety oversight.
	Paragraph 2	The purpose for the duplicative protocol processes for NIH are attributed to provide a forum for open dialogue and transparency. This stated purpose does not include the oversight for biosafety.	Explicitly state how biosafety will be maintained for HGT clinical research studies under these changes.	Omission of biosafety, as a purpose included in the NIH oversight to protect the research worker, the public, and the environment, is misleading with regard to priorities.
	Paragraph 3	The 2014 Institute of Medicine of the National Academies report, *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee* , is dated.	Maintain the RAC to review research (including clinical research) that merits review. This should be defined to include clinical research involving emerging technologies and research impacted by recent scientific findings.	The recommendations for oversight of rapidly emerging technologies that are now moving into clinical research may no longer be appropriate.
	Paragraph 6	Paragraph states that IBC safety reporting is complete once last participant is administered the final dose of the product.	Include longer reporting time frame; adverse events may not be immediately foreseen.	Reporting should include the proposed study time for follow-up and not the last dosing.

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Section Name or #	*Paragraph or #*	*Text at issue*	*Proposed change*	*Comment*
	Paragraph 6	With the proposed elimination of the requirements for safety reporting under Appendix M, IBC oversight should be completed immediately after the last participant is administered the final dose of product. Additionally, the role of IBC review is proposed to be amended to be consistent with FDA's current guidance regarding individual patient expanded access to investigational drugs. In this way, the role of the IBCs will be focused on providing local biosafety oversight of basic and clinical research involving recombinant or synthetic nucleic acids.	Clarify the specific application of the safety reporting under the context of clinical trial progression. Clarify also the integration of the amendment wih the FDA guidance cited, and provide the link to the specific guidance document.	Please clarify: the proposed requirement of IBC oversight seems redundant to 21 CFR 312.21 Phases of an investigation (b) and also 21 CFR 312.32 IND safety reporting.
	Paragraph 6	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.	Clarification is needed regarding expectations of the IBCs.	

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Section Name or #	*Paragraph or #*	*Text at issue*	*Proposed change*	*Comment*
Section I-A-1-a	Paragraph 1	The new wording removes the statement "Institutional Review Board (IRB) approval has been obtained."	Keep the wording in paragraph 1 stating "Institutional Review Board (IRB) approval has been obtained."	De-linking IRB approval and IBC approval, and the clinical trial from the experiment (introduction of rsNA into an organism), could lead to progression of clinical trial up to the point of injection and pose an undue burden on an IBC to approve research following already expended funds and human subject enrollment.
Section I-A-a-1	First sentence	Proposed test states to refer to Section I-E-7 for the definition of initiation; Section I-E-7 is proposed to be eliminated.	Correct proposed text to refer to Section I-E-4 as amended.	Corrected text: "no human gene transfer experiment shall be initiated (see "definition of initiation in Section I-E-4) until Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained;"
Section III-A		No provision remains with complete removal of RAC for Major/Minor Actions.	Replace the requirement for RAC review with potential for RAC consideration.	
Section III	Paragraph 1, (iii)	The revised wording removes "Institutional Review Board Approvals"	Keep the wording regarding "Institutional Review Board Approvals".	Recommend not siloing the IBC and IRB. Communication should be encouraged to promote an overall culture of safety.
Section III-C	Title			
Section III-C-1	Paragraph 5	The revised wording removes the statement "Institutional Review Board (IRB) approval has been obtained."		

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Section Name or #	*Paragraph or #*	*Text at issue*	*Proposed change*	*Comment*
Section III-C-1	Paragraph 3 (revised)	Definition of Individual patient expanded access IND is missing.	Include definition and justification as to why this research should be exempt under the *NIH Guideline.*	Evaluation needed (by the RAC) to determine if research under this category is not pertinent to the NIH Guidelines. Processes for this specific research category could be modified to avoid any negative impact to treatment; such as in modifying FDA form for biosafety oversight and RAC review.
Section III-C-1	Several paragraphs	Removal of several paragraphs after the definition of HGT. One paragraph has the language from the 2016 amendment including initial site and the IBC obligation to request RAC review.	OSP needs to clarify whether initial site review by IBC/IRB is required for HGT studies.	
Section IV-B-2-b-(1)	(vii)	Reporting of serious adverse effects to OSP during studies involving recombinant or synthetic nucleic acids.	(vii) seems to be removed and includes adverse events reporting- if removed, the functions of the IBC need to be clearly stated that it will not be responsible for reporting SAEs.	Incident reports should continue to NIH, via the the RAC, and not just the OSP. Not enough is known to stop adverse reporting as practiced under the 2016 *NIH Guidelines* .
Section IV-B-2-b-(1)	(iii)	These sections remove all references to Appendix M, but Appendix M can be converted to a useful tool for investigators.	Suggest keeping reference to Appendix M, but amending Appendix M to be guidance document for IBC submission of HGT protocols.	While Appendix M is removed under the proposed amendment, the required documents have provided key information for IBC review. Appendix M should be amended to make that needed information clear to the investigator and easy to find for the reviewer.
Section IV-B-6	(ii)			
Section IV-B-7	Paragraph 1			

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Section Name or #	*Paragraph or #*	*Text at issue*	*Proposed change*	*Comment*
Section IV-B-7-e(5)		This section refers to reporting requirements for HGT protocols in compliance with the *NIH Guidelines* as stated in Appendix M.	Reporting requirements should remain in place, but revised to exclude RAC reporting to match the proposed amendment, or amended to meet revised requirements of the RAC should it be retained.	Incidents, exposures, or serious adverse events should still be reported to NIH. NIH OSP should be made aware of any SAE involving rDNA in a trial.
IV-C-1; IV-C-3		Information in these sections refer to OSP as strictly administrative.	Create section within OSP or functioning alongside that is able to provide the scientific and ethical review.	Recommend clarifying earlier in the NIH Guidelines who will be conducting the scientific and ethical reviews and the required qualifications.
IV-C-2		Entire section	Recommend retaining the RAC and revising description to meet outcome desired.	Retaining the RAC is recommended by biosafety professionals. Revision of this section and the RAC Charter to describe the RAC agenda and process for solicitation is needed.
IV-C-3-a		Gene editing for HGT does not appear to be considered for review.	Maintain RAC at a minimum for gene editing HGT.	Refer to entire comments submitted for additional research fields to be covered by the RAC.
Section V	Paragraph V-B	Recommend adding clarification for investigator designation of exempt research.	Add: “Research identified as exempt by a PI should be reviewed by the BSO and/or the IBC for accurate identification under Section III.”	Added text will clarify the expected oversight for exempt designation for the PI.

Submission #34

Date	10/17/2018
Name:	Meagan Fitzpatrick
Organization:	Georgia Tech
Email:	meagan.fitzpatrick@ehs.gatech.edu
Comment:	Please see attached.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/FederalRegisterResponseLetter_83FR41082_10-2018.pdf

Environmental Health and Safety
793 Marietta Street NW
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October 16, 2018

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

RE: 83 FR 41082 "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)"

Dear Director,

Georgia Institute of Technology (Georgia Tech) values the opportunity to provide comments on the recently proposed changes to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*) published in the Federal Register on August 17, 2018 (83 FR 41082).

The Georgia Tech Institutional Biosafety Committee (IBC) reviewed, met and discussed these proposed changes to the *NIH Guidelines* on September 28, 2018. The Georgia Tech IBC also reviewed the Federal Register response letter and referenced comments table distributed by the American Biological Safety Association (ABSA) International to its members on October 9, 2018 (see Attachments 1 and 2 respectively).

ABSA International, founded in 1984, serves to promote biosafety as a scientific discipline by providing a professional association that represents the interests and needs of biosafety practitioners both in the United States and abroad.

This letter serves to indicate Georgia Tech's support and agreement with the comments provided by ABSA to the changes proposed to the *NIH Guidelines*.

Thank you for the opportunity to review the proposed changes to the NIH Guidelines. Please contact me with any questions.

Best regards,

Meagan Fitzpatrick, MPH
Biosafety Officer
Environmental Health and Safety
Georgia Institute of Technology
Meagan.fitzpatrick@ehs.gatech.edu
404-894-6120

Date

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

RE: 83 FR 41082 "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)"

Dear Director,

The American Biological Safety Association (ABSA) International welcomes the opportunity to comment on the "*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)" published 17 August 2018. ABSA International provides a critical expertise for this topic as many of its members are extensively involved in implementing the *NIH Guidelines* and fulfilling certain roles therein.

There is one overarching and pervasive concern expressed by biosafety professionals:

Concern: Eliminating the Recombinant DNA Advisory Committee (RAC) from performing a transparent and scientific review of Human Gene Transfer (HGT) clinical trials is of great concern and deemed inadvisable. Removing the RAC, a body of world-class experts, from being an integrated and defined component of NIH research oversight for recently emerged and emerging technologies has a negative impact on the safe conduct of research.

Recommendation: Continue RAC review for emerging and recently emerged technologies, for Phase I and first in human use research, for decisions regarding major actions, and for monitoring incident reports. Use this opportunity to detail a process for the NIH Director, and for Institutional Biosafety Committees (IBC) and investigators to solicit input from this committee of world-class experts. Revise the *NIH Guidelines*, the RAC Charter, and other pertinent documents accordingly and release for public review and comment.

Why keep the RAC?

The RAC is a body with technical expertise of a scale and breadth rarely accessible to research entities. While gene therapy, gene transfer, and gene editing technologies have moved from being an emerging technology to emerged in their biotechnology and clinical applications, as

specified by the NIH Director and FDA Commissioner, the move to clinical research is recent. The emergence of CRISPR and CAR-T technologies opened the door to a wide variety of clinical applications yet we are still learning more about these technologies and their associated risks. The collective expertise on the RAC was invaluable in the review of novel, complex technologies and would continue to be so in this role, as well as in the continued review of recently emerged technologies. The exercise of RAC member responsibilities itself functions to continuously raise the level of expertise of its members and enables a holistic assessment for the multiple components participating in, or potentially affected by, research.

Transparency in the process for soliciting RAC input, by inclusion in the *NIH Guidelines*, will continue to promote research rigor in study design and safety for all persons involved. The description for the RAC to exist as an advisory body in this subsequent proposed amendment to the *NIH Guidelines* is not sufficiently specific to be informative. It is unclear what the agenda will be for the RAC once it is removed from the *NIH Guidelines*. The plan for removal of the RAC, and for decisions previously made by the RAC to rest with the NIH Director and the Office of Science Policy (OSP), are of great concern particularly with regard to Major Actions (Section III-A-1). Decisions for research involving risk at the level of a Major Action should require expertise and input from the RAC, in a manner transparent to the public and in a procedure consistently applied.

Concerns for the changing role of the RAC regarding adequate review and research oversight persist from the those raised in comment to 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, submitted by ABSA International on November 30, 2015, for what became the April 2016 Amendment. Changes to diminish the role of the RAC made in the 2016 *NIH Guidelines* amendment were substantial, significant, and unfortunately sufficiently recent to preclude an evaluation of the effect of those changes.

Institutional Biosafety Committees

Institutional Biosafety Committees (IBC) are concerned that there is no formal mechanism remaining in the amendment for the IBC to seek guidance from the RAC on specific concerns that arise during the review process. Previously, the referral of protocols for public RAC reviews served this purpose for the numerous institutions whose research calls for registered IBCs. The absence of the RAC's involvement in clinical research oversight is already being observed, restricting access to pertinent expertise not widely available, *prior* to completion of public review and official implementation of the proposed amendment.

Many IBCs, excluding the long-standing academic medical centers traditionally at the forefront of gene therapy, lack the expertise to adequately conduct a risk assessment for clinical research as applied in pharmacy and clinical settings; and conversely, risk assessments and research

oversight in clinics and hospitals differ vastly from the application of the *NIH Guidelines* and biosafety principles seen in the conduct of relevant pre-clinical research.

According to the NIH Office of Science Policy (OSP, 26 August 2018), the last 10 years has seen a 59% increase in IBC registrations, which illustrates the rapid growth of this exciting clinical application. The majority of these IBCs are for locations which review HGT clinical research. For many locations, pharmacy and clinical staff have little to no experience in biosafety/biosurety and view the handling of HGT products akin to chemotherapy. The safe conduct of HGT trials requires appropriate risk assessments and significant education, particularly pertaining to the replication competent biologicals being utilized. Research test articles and technologies applied to human subjects retain the risks specific to the material involved, and potential risks are increasingly being reported (e.g., CAR-T cytokine release syndrome, additional CRISPR off-target effects, and significant genomic damage following CRISPR-Cas9 nucleic acid break repair). The expertise of the RAC is clearly needed to provide far-reaching support for the safe research of these emerging and recently emerged technologies.

Justification for Change

Justification for eliminating RAC review is drawn from comparing the oversight of HGT studies to other areas of clinical research; however, not all clinical research studies pose the same types of risk.

Similarly, not all oversight bodies share the same focus on research. All layers of oversight protect different portions of a 360° view of clinical research and each have their importance.

Review by one body such as the RAC for ethical, scientific, and risk assessment of HGT research is outside the FDA purview, and would remain beneficial.

Removing redundancy in research protocol processes is a good goal, but should not be done at the expense of reducing safety. Returning the mission of the RAC to its original purpose, belies the progress and refinement of the RAC duties to meet needs later identified. Returning to the past is not preparing for the future.

Decreasing the Research Burden is Supported Overall

Biosafety professionals generally support and embrace the spirit of the proposed amendment to the *NIH Guidelines* to further streamline the processes for research oversight for HGT clinical trials. The efficiencies gained in removing duplicative steps decreases the research burden and may clarify for investigators the focus of oversight bodies involved in reviewing HGT clinical applications. Removing the requirement to complete Appendix M, allows for less redundancy and confusion between the IBC and the IRB. The documents required under Appendix M have

been very helpful for IBC review, pulling out information on the study drug, personnel involvement, and trial logistics. Obtaining the pertinent information is still valuable for biosafety review and identification of containment and training needs. Conversion of Appendix M to a guidance document with significant narrowing to highlight the relevant information is encouraged.

Additional Comments

Please review the additional comments provided in the attached Excel table. Observations fall into general comments and those pertinent to specific proposed text. Issues include, but are not limited to: gaps in oversight that arise with the proposed amendment, additional RAC concerns, proposals, and errors/omissions in the proposed text.

ABSA International appreciates the opportunity to review the proposed amendment to the NIH Guidelines. The comments provided are respectfully offered for your consideration.

Please contact me with any questions or to request clarification.

Respectfully,

Patrick Condreay, PhD, RBP
President, ABSA International

ABSA International

Document: "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)"	**Document Citation/Number: 83 FR 41082** https://www.federalregister.gov/documents/2018/08/17/2018-17760/national-institutes-of-health-nih-office-of-science-policy-osp-recombinant-or-synthetic-nucleic-acid https://www.gpo.gov/fdsys/pkg/FR-2018-08-17/pdf/2018-17760.pdf

Table 1: General Comments

Observation/Concern	*Comment*	*Proposed change*
There is a gap in oversight of human gene transfer clinical studies under the current proposal.	Registration of Phase 1 studies is not mandatory on ClinicalTrials.gov as these studies do not meet the definition of an applicable clinical trial (ACT) as defined in section 402(j) of the PHS Act. ClinicalTrials.gov does not provide an adequate measure of oversight or transparency as clinical trial registration is not required until 21 days after enrolling the first human subject.	Maintain RAC for review of Phase I trials that meet the current criteria
A loophole exists in oversight of human gene transfer clinical studies under the current proposal.	Under FDAAA 801, the manufacture of a drug, biological, or device product in the US renders the study to be an ACT. A drug or biological product manufactured outside the US could be used and would not fall under FDAAA 801.	Expand scope of FDAAA 801 to include products manufactured outside of the US
Reducing duplications in submissions to the FDA and NIH could be met following a process similar to that in the European Union (EU) where registration of clinical trials are harmonized among multiple interests.	Use of FDA forms for both NIH and FDA purposes. FDAAA801 will need to be updated to reflect any changes to NIH Guidelines	Maintain registering with NIH but allow for the use of FDA forms; expand scope of FDA forms to include risk assessment questions similar to EU registering requirements
Proposed RAC focus to emerging technologies will miss newly identified risks that impact current research	Proposed text shifts the focus of the RAC to emerging biotechnologies only; it is not stated to continue review of current research protocols in the new system. Example concerns: (1) Existing biotechnology (e.g. CRISPR/Cas 9) are now being used in humans without knowledge of off-target impact; (2) Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements (Kosicki, 2018)	Maintain, and potentially increase, RAC focus to continue evaluating risks in research involving existing and emerging biotechnology

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Proposed changes may lead to dissolution of the RAC, and remove a national resource for research.	Removal of the RAC from the Guidelines, in conjunction with a 2-year revolving charter may lead to the dissolution of the committee even with its authorization in the Public Health Service Act. RAC charter will need to be updated for revised role and include recommended and responsive changes for continued role in research oversight.	Propose changes to the RAC charter and oversight be made that are responsive to stated concerns; that the NIH Director solicit input from impacted and involved parties; and that the draft charter and oversight be released to the public for review and comment.
What is the mechanism by which the NIH Director can solicit advice from the RAC? What is the mechanism for the IBC?	Inclusion of the process for soliciting input from the RAC on research protocols provide assurance to principal investigators and research entities of review by multiple world-class experts in their field. Transparency in this process for soliciting RAC input will continue to promote research rigor in study design and safety for all persons involved.	Do not eliminate every mention of the RAC from the Guidelines; maintain the RAC for Phase I and first in human research.
There is the potential that not all local IBCs and IRBs have the knowledge to address all the unknowns present.	The rapid growth of research involving nucleic acids and the conduct of human gene transfer studies outpaces the expertise available for service on IBCs. Few, if any, institutions would have IBC members with technical expertise at the level of members of the RAC.	Maintain registration with the NIH for review of projects of recombinant nature to ensure experts in this field have one central clearing house; clinicaltrials.gov is a central database but does not offer the same transparency for IBCs.

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There needs to be an option/requirement for Major Action, including HGT, to ensure applicable research goes back to NIH OSP for RAC review.		The criteria from the 2016 amendment should be added as to when the study would benefit from RAC review.		Include "New technologies; use of new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk; study relies on preclinical safety data that were obtained using a new preclinical model of unknown and unconfirmed value; or the proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate protocol rigorously;" as text to identify research areas subject to RAC review.
Appendix M has aided in assessing biosafety risks, identifying opportunities for mitigation, and determing training needs. Appendix M may serve a useful role even if deleted from the NIH Guidelines.		The IBC will continue to focus on worker safety with removal of Appendix M, and conduct thorough site-specific reviews as conducted for other protocols. The use of Appendix M has provided important details for the risk assessment of clinical research, including the observation that pharmacy and clinical staff have little to no experience on biosafety, disinfection, personal protective equipment, and engineering controls. The significant need for substantial training is commonly observed for the safe conduct of clinical trials.		Propose Appendix M be converted to a guidance document following revision.
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IV-C-2		Entire section	Recommend retaining the RAC and revising description to meet outcome desired.	Retaining the RAC is recommended by biosafety professionals. Revision of this section and the RAC Charter to describe the RAC agenda and process for solicitation is needed.
IV-C-3-a		Gene editing for HGT does not appear to be considered for review.	Maintain RAC at a minimum for gene editing HGT.	Refer to entire comments submitted for additional research fields to be covered by the RAC.
Section V	Paragraph V-B	Recommend adding clarification for investigator designation of exempt research.	Add: "Research identified as exempt by a PI should be reviewed by the BSO and/or the IBC for accurate identification under Section III."	Added text will clarify the expected oversight for exempt designation for the PI.

Submission #35

Date	10/19/2018
Name:	Ed R Blazek
Organization:	Rush
Email:	Ed_R_Blazek@rush.edu
Comment (limit: 15,000 characters):	Please see attached.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/Appendix_M_Suspension_Comment_Rush10-16-18.pdf

October 15, 2018

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

Dear Director:

We are concerned by the August 16, 2018 suspension of major provisions of Appendix M of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)* governing human gene transfer research.[1] We believe that these proposed changes could have negative effects on the development of gene transfer for treatment of human disease and on the status of the *NIH Guidelines* as a scientifically enlightened code of conduct for this research.

Carcinogenesis is an inherent danger of certain methods of gene transfer and other genetic manipulations. With the suspension of Appendix M1C4 safety reporting, the best opportunity to detect modest increases in carcinogenesis among participants of multisite gene transfer trials has been surrendered. Few, if any, individual study sites will enroll enough subjects to yield a statistically detectable signal of carcinogenesis, unless cancer risk is so greatly elevated that almost *all* local subjects of such a trial develop cancer within year or two of treatment. Cessation of safety reporting may have been proposed in part because sparse or incomplete data have been received by the NIH Office of Science Policy (OSP). Rather than abandon the effort, however, the *NIH Guidelines* could be changed to strengthen safety reporting rules by, for example:

(1) Stating explicitly that all new post-treatment cancers during the treatment or follow-up periods must be reported to the OSP. This would eliminate long-standing ambiguity about which adverse events ought to be reported.
(2) Requiring periodic submission of a statement of adverse events (or their absence) directly from every site's *registered* lead investigator. In retrospect, permitting the delegation of the safety reporting to a third party (Appendix M-1-C-4) whose financial interest is in conflict with rigorous safety reporting was a recipe for failure, as the opioid prescription drug crisis has demonstrated.

Collection of these data would be pointless, however, without their analysis and publication. To revitalize safety reporting, the OSP must obtain the resources for expert analysis of these data and commit publicly to their periodic publication, giving clinical investigators an intellectual motivation for compliance. Delayed recognition of carcinogenesis or other harmful late effects of gene transfer could damage the field much as did the tragic acute death of Jesse Gelsinger in 1999.

The proposed changes limit the Recombinant DNA Advisory Committee (RAC) to a policy advisory role with no capability, even under exceptional circumstances, to deliberate as a body of

experts and advise on specific projects that are believed by local IBCs to be of elevated risk. Because CRISPR/Cas9, CAR-T and other new technologies show great promise, the number and sophistication of these trials will rapidly increase. Our IBC, like many others, has reviewed various innovative projects that strain the risk assessment capacity of its membership. External experts are identifiable from their publications, but these persons are almost certainly competitors of the local PI who are in a position to take advantage of a detailed consultation. This fact deters local IBCs from involving individual external reviewers. External review of a project requested by the local IBC is a role that has been and could again be performed by an unfettered RAC, with its depth of scientific expertise and mutual oversight by committee members to lessen the chance that unpublished information and concepts are misused. As an unintended consequence of the proposed change, we fear that it will weaken the RAC even as a policy advisory committee--with its authority to review individual projects removed, we predict that its level of technical expertise will steadily erode through disuse, with deleterious effects on its residual role.

The evolution of the *NIH Guidelines* from the 1975 Asilomar meeting as conceived and organized by early developers of genetic engineering has long been considered an exemplar of enlightened scientific self-regulation, giving investigators confidence that there was a sound scientific basis for recombinant DNA regulation. The August 16 proposed changes of Appendix M did not involve broad, public prior consultation with either practitioners or regulators of recombinant DNA. This is an unusual--perhaps unprecedented—process for revising biomedical regulation in the U.S. Will the proposed changes made in this manner, at this pivotal juncture in the development of the technology, be recognized by all as appropriately reflecting risks and benefits of gene transfer? We worry that these changes could erode the confidence of investigators and/or regulators in the *NIH Guidelines* going forward. Whether the August 16 proposed changes of the *NIH Guidelines* are adopted as currently written or are ultimately modified, we hope that these and future proposed changes in the *NIH Guidelines* will be discussed among all affected parties prior to adoption.

Sincerely,

Ed R. Blazek, Ph.D., Biological Safety Officer
Amarjit Virdi, Ph.D., IBC Chair
On behalf of members of the Rush University
Medical Center Institutional Biosafety Committee

[1]83 FR 41082 "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)"

Submission #36

Date	10/20/2018
Name:	William L. Freeman
Organization:	Northwest Indian College
Email:	wfreeman@nwic.edu
Comment:	I agree with the NOT-OD-18-218 that redundant and duplicative reviews should be eliminated. However, as expressed and proposed, the NOT-OD-18-218 has two major flaws – flaws so serious that I consider them to be fatal flaws. 1] The NOT-OD-18-218 proposes that we accept both its proposed changes change in the RAC, plus has a promised revised "RAC" — but without revealing what that revised RAC will be in detail. (In the vernacular, such a sale is called being asked to "buy a pig in a poke.") 2] The National Academies Press published in 2017 the report by the Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations titled Human Genome Editing: Science, Ethics, and Governance. The NOT-OD-18-218 proposes to totally ignore or reject that Committee's five strong recommendations, numbers 7.1 to 7.5, in Chapter 7 in the 2017 National Academies Press publication. Your proposal provides not a single substantive reason to ignore or reject those 5 strong recommendations, in either the proposal itself or the article in the New England Journal of Medicine by Dr. Francis S. Collins and Dr. Scott Gottlieb. Your proposal did not even cite the 2017 publication that was and is both authoritative (as National Academies Press usually are), and also is highly relevant to your proposal – a fatal omission. I strongly recommend that NIH start over and resubmit a proposal that does not include the two flaws I cite.

Submission #37

Name:	10/22/2018 Marian Downing
Organization:	ABSA International
Email:	(b)(6) - Personal Info@gmail.com
Comment:	To Whom it May Concern: I endorse the attached letter concerning the proposed changes to the NIH Guidelines and the Final Draft Comments from ABSA International.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	

ABSA International

Document:	Document Citation/Number: 83 FR 41082
"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)"	https://www.federalregister.gov/documents/2018/08/17/2018-17760/national-institutes-of-health-nih-office-of-science-policy-osp-recombinant-or-synthetic-nucleic-acid
	https://www.gpo.gov/fdsys/pkg/FR-2018-08-17/pdf/2018-17760.pdf

Table 1: General Comments

Observation/Concern	*Comment*	*Proposed change*
There is a gap in oversight of human gene transfer clinical studies under the current proposal.	Registration of Phase 1 studies is not mandatory on ClinicalTrials.gov as these studies do not meet the definition of an applicable clinical trial (ACT) as defined in section 4020) of the PHS Act. ClinicalTrials.gov does not provide an adequate measure of oversight or transparency as clinical trial registration is not required until 21 days after enrolling the first human subject.	Maintain RAC for review of Phase I trials that meet the current criteria
A loophole exists in oversight of human gene transfer clinical studies under the current proposal.	Under FDAAA 801, the manufacture of a drug, biological, or device product in the US renders the study to be an ACT. A drug or biological product manufactured outside the US could be used and would not fall under FDAAA 801.	Expand scope of FDAAA 801 to include products manufactured outside of the us
Reducing duplications in submissions to the FDA and NIH could be met following a process similar to that in the European Union (EU) where registration of clinical trials are harmonized among multiple interests.	Use of FDA forms for both NIH and FDA purposes. FDAAA801 will need to be updated to reflect any changes to NIH Guidelines	Maintain registering with NIH but allow for the use of FDA forms; expand scope of FDA forms to include risk assessment questions similar to EU registering requirements
Proposed RAC focus to emerging technologies will miss newly identified risks that impact current research	Proposed text shifts the focus of the RAC to emerging biotechnologies only; it is not stated to continue review of current research protocols in the new system. Example concerns: (1) Existing biotechnology (e.g. CRISPR/Cas 9) are now being used in humans without knowledge of off-target impact; (2) Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements (Kosicki, 2018)	Maintain, and potentially increase, RAC focus to continue evaluating risks in research involving existing and emerging biotechnology

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Proposed changes may lead to dissolution of the RAC, and remove a national resource for research.	Removal of the RAC from the Guidelines, in conjunction with a 2-year revolving charter may lead to the dissolution of the committee even with its authorization in the Public Health Service Act. RAC charter will need to be updated for revised role and include recommended and responsive changes for continued role in research oversight.	Propose changes to the RAC charter and oversight be made that are responsive to stated concerns; that the NIH Director solicit input from impacted and involved parties; and that the draft charter and oversight be released to the public for review and comment.
What is the mechanism by which the **NIH** Director can solicit advice from the RAC? What is the mechanism for thelBC?	Inclusion of the process for soliciting input from the RAC on research protocols provide assurance to principal investigators and research entities of review by multiple world-class experts in their field. Transparency in this process for soliciting RAC input will continue to promote research rigor in study design and safety for all persons involved.	Do not eliminate every mention of the RAC from the Guidelines; maintain the RAC for Phase I and first in human research.
There is the potential that not all local IBCs and IRBs have the knowledge to address all the unknowns present.	The rapid growth of research involving nucleic acids and the conduct of human gene transfer studies outpaces the expertise available for service on IBCs. Few, if any, institutions would have IBC members with technical expertise at the level of members of the RAC.	Maintain registration with the NIH for review of projects of recombinant nature to ensure experts in this field have one central clearing house; clinicaltrials.gov is a central database but does not offer the same transparency for IBCs.

There needs to be an option/requirement for Major Action, including HGT, to ensure applicable research goes back to NIH OSP for RAC review.	The criteria from the 2016 amendment should be added as to when the study would benefit from RAC review.	Include "New technologies; use of new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk; study relies on preclinical safety data that were obtained using a new preclinical model of unknown and unconfirmed value; or the proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate protocol rigorously;" as text to identify research areas subject to RAC review.
Appendix M has aided in assessing biosafety risks, identifying opportunities for mitigation, and determing training needs. Appendix M may serve a useful role even if deleted from the NIH Guidelines.	The IBC will continue to focus on worker safety with removal of Appendix M, and conduct thorough site-specific reviews as conducted for other protocols. The use of Appendix M has provided important details for the risk assessment of clinical research, including the observation that pharmacy and clinical staff have little to no experience on biosafety, disinfection, personal protective equipment, and engineering controls. The significant need for substantial training is commonly observed for the safe conduct of clinical trials.	Propose Appendix M be converted to a guidance document following revision.

Table 2: Specific Comments

section ;ame or Paragraph or#	*Text at issue*	*Proposed change*	*Comment*

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Section Name or II	Paragraph or#	Text at issue	Proposed change	Comment
	Paragraph 1	"Oversight mechanisms for ensuring HGT proceeds safely" are stated to "have sufficiently evolved to keep pace with new discoveries in this field." How was the sufficiency determined?	Define and describe "sufficient oversight". Include argument and references to support the characterization as sufficient oversight.	HGT clinical research differs from other clinical research. It is a relatively new field and oversight should continue to have unique mechanisms as clinical research proceeds. There is some precedent as clinical research involving radioactive materials as a research component should include radiation safety oversight.
	Paragraph 2	The purpose for the duplicative protocol processes for NIH are attributed to provide a forum for open dialogue and transparency. This stated purpose does not include the oversight for biosafety.	Explicitly state how biosafety will be maintained for HGT clinical research studies under these changes.	Omission of biosafety, as a purpose included in the NIH oversight to protect the research worker, the public, and the environment, is misleading with regard to priorities.
	Paragraph 3	The 2014 Institute of Medicine of the National Academies report, *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee,* is dated.	Maintain the RAC to review research (including clinical research) that merits review. This should be defined to include clinical research involving emerging technologies and research impacted by recent scientific findings.	The recommendations for oversight of rapidly emerging technologies that are now moving into clinical research may no longer be appropriate.
SUPPLEMENTARY INFORMATION	Paragraph 6	Paragraph states that IBC safety reporting is complete once last participant is administered the final dose of the product.	Include longer reporting time frame; adverse events may not be immediately foreseen.	Reporting should include the proposed study time for follow-up and not the last dosing.

5ection ;ame or	*Paragraph or#*	*Text at issue*	*Proposed change*	*Comment*
	Paragraph 6	With the proposed elimination of the requirements for safety reporting under Appendix M, IBC oversight should be completed immediately after the last participant is administered the final dose of product. Additionally, the role of IBC review is proposed to be amended to be consistent with FDA's current guidance regarding individual patient expanded access to investigational drugs. In this way, the role of the IBCs will be focused on providing local biosafety oversight of basic and clinical research involving recombinant or synthetic nucleic acids.	Clarify the specific application of the safety reporting under the context of clinical trial progression. Clarify also the integration of the amendment wih the FDA guidance cited, and provide the link to the specific guidance document.	Please clarify: the proposed requirement of IBC oversight seems redundant to 21 CFR 312.21 Phases of an investigation (b) and also 21 CFR 312.32 IND safety reporting.
	Paragraph 6	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.	Clarification is needed regarding expectations of the IBCs.	

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Section Name or II	Paragraph or#	Text at issue	Proposed change	Comment
Section I-A-1-a	Paragraph 1	The new wording removes the statement "Institutional Review Board (IRB) approval has been obtained."	Keep the wording in paragraph 1 stating "Institutional Review Board (IRB) approval has been obtained."	De-linking IRB approval and IBC approval, and the clinical trial from the experiment (introduction of rsNA into an organism), could lead to progression of clinical trial up to the point of injection and pose an undue burden on an IBC to approve research following already expended funds and human subject enrollment.
Section I-A-a-1	First sentence	Proposed test states to refer to Section I-E-7 for the definition of initiation; Section I-E-7 is proposed to be eliminated.	Correct proposed text to refer to Section I-E-4 as amended.	Corrected text: "no human gene transfer experiment shall be initiated (see "definition of initiation in Section I-E-4) until Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained;"
Section III-A		No provision remains with complete removal of RAC for Major/Minor Actions.	Replace the requirement for RAC review with potential for RAC consideration.	
Section III	Paragraph 1, (iii)	The revised wording removes "Institutional Review Board Approvals"	Keep the wording regarding "Institutional Review Board Approvals".	Recommend not siloing the IBC and IRB. Communication should be encouraged to promote an overall culture of safety.
Section 111-C	Title			
Section 111-C-1	Paragraph 5	The revised wording removes the statement "Institutional Review Board (IRB) approval has been obtained."		

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Section ;ame or	*Paragraph or#*	*Text at issue*	*Proposed change*	*Comment*
Section III-C-1	Paragraph 3 (revised)	Definition of Individual patient expanded access IND is missing.	Include definition and justification as to why this research should be exempt under the *NIH Guideline.*	Evaluation needed (by the RAC) to determine if research under this category is not pertinent to the NIH Guidelines. Processes for this specific research category could be modified to avoid any negative impact to treatment; such as in modifying FDA form for biosafety oversight and RAC review.
Section III-C-1	Several paragraphs	Removal of several paragraphs after the definition of HGT. One paragraph has the language from the 2016 amendment including initial site and the IBC obligation to request RAC review.	OSP needs to clarify whether initial site review by IBC/IRB is required for HGT studies.	
Section IV-B-2-b-(1)	(vii)	Reporting of serious adverse effects to OSP during studies involving recombinant or synthetic nucleic acids.	(vii) seems to be removed and includes adverse events reporting- if removed, the functions of the IBC need to be clearly stated that it will not be responsible for reporting SAEs.	Incident reports should continue to NIH, via the the RAC, and not just the OSP. Not enough is known to stop adverse reporting as practiced under the 2016 *NIH Guidelines* .
Section IV-B-2-b-(1)	(iii)	These sections remove all references to Appendix M, but Appendix M can be converted to a useful tool for invpc;tig-;itorc;_	Suggest keeping reference to Appendix M, but amending Appendix M to be guidance document for IBC submission of HGT nrntoc:olc;_	While Appendix M is removed under the proposed amendment, the required documents have provided key information for IBC review. Appendix M should be amended to make that nPPrlPrl infnrm;ition rlP;ir to thP
Section IV-B-6	(ii)			

Section Name or 11	Paragraph or#	Text at issue	Proposed change	Comment
Section IV-B-7	Paragraph 1			investigator and easy to find for the reviewer.
Section IV-B-7-e(S}		This section refers to reporting requirements for HGT protocols in compliance with the *NIH Guidelines* as stated in Appendix M.	Reporting requirements should remain in place, but revised to exclude RAC reporting to match the proposed amendment, or amended to meet revised requirements of the RAC should it be retained.	Incidents, exposures, or serious adverse events should still be reported to NIH. NIH OSP should be made aware of any SAE involving rDNA in a trial.
IV-C-1; IV-C-3		Information in these sections refer to OSP as strictly administrative.	Create section within OSP or functioning alongside that is able to provide the scientific and ethical review.	Recommend clarifying earlier in the NIH Guidelines who will be conducting the scientific and ethical reviews and the required qualifications.
IV-C-2		Entire section	Recommend retaining the RAC and revising description to meet outcome desired.	Retaining the RAC is recommended by biosafety professionals. Revision of this section and the RAC Charter to describe the RAC agenda and process for solicitation is needed.
IV-C-3-a		Gene editing for HGT does not appear to be considered for review.	Maintain RAC at a minimum for gene editing HGT.	Refer to entire comments submitted for additional research fields to be covered by the RAC.
Section V	Paragraph V-B	Recommend adding clarification for investigator designation of exempt research.	Add: "Research identified as exempt by a PI should be reviewed by the BSO and/or the IBC for accurate identification under Section III."	Added text will clarify the expected oversight for exempt designation for the PI.

Submission #38

Date	10/22/2018
Name:	Hallie Hoskins
Organization:	University of Oregon
Email:	hallieh@uoregon.edu
Comment:	Dear Director, Thank you for the opportunity to comment on the "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)" published 17 August 2018. There is one overarching and pervasive concern I share with my fellow biosafety professionals: Concern: Eliminating the Recombinant DNA Advisory Committee (RAC) from performing a transparent and scientific review of Human Gene Transfer (HGT) clinical trials is of great concern and deemed inadvisable. Removing the RAC, a body of world-class experts, from being an integrated and defined component of NIH research oversight for recently emerged and emerging technologies has a negative impact on the safe conduct of research. Recommendation: Continue RAC review for emerging and recently emerged technologies, for Phase I and first in human use research, for decisions regarding major actions, and for monitoring incident reports. Use this opportunity to detail a process for the NIH Director, and for Institutional Biosafety Committees (IBC) and investigators to solicit input from this committee of world-class experts. Revise the NIH Guidelines, the RAC Charter, and other pertinent documents accordingly and release for public review and comment. Why keep the RAC? The RAC is a body with technical expertise of a scale and breadth rarely accessible to research entities. While gene therapy, gene transfer, and gene editing technologies have moved from being an emerging technology to emerged in their biotechnology and clinical applications, as specified by the NIH Director and FDA Commissioner, the move to clinical research is recent. The emergence of CRISPR and CAR-T technologies opened the door to a wide variety of clinical applications yet we are still learning more about these technologies and their associated risks. The collective expertise on the RAC was invaluable in the review of novel, complex technologies and would continue to be so in this role, as well as in the continued review of recently

emerged technologies. The exercise of RAC member responsibilities itself functions to continuously raise the level of expertise of its members and enables a holistic assessment for the multiple components participating in, or potentially affected by, research. Transparency in the process for soliciting RAC input, by inclusion in the NIH Guidelines, will continue to promote research rigor in study design and safety for all persons involved. The description for the RAC to exist as an advisory body in this subsequent proposed amendment to the NIH Guidelines is not sufficiently specific to be informative. It is unclear what the agenda will be for the RAC once it is removed from the NIH Guidelines. The plan for removal of the RAC, and for decisions previously made by the RAC to rest with the NIH Director and the Office of Science Policy (OSP), are of great concern particularly with regard to Major Actions (Section III-A-1). Decisions for research involving risk at the level of a Major Action should require expertise and input from the RAC, in a manner transparent to the public and in a procedure consistently

Concerns for the changing role of the RAC regarding adequate review and research oversight persist from the those raised in comment to 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, submitted by ABSA International on November 30, 2015, for what became the April 2016 Amendment. Changes to diminish the role of the RAC made in the 2016 NIH Guidelines amendment were substantial, significant, and unfortunately

Institutional Biosafety Committees (IBC) are concerned that there is no formal mechanism remaining in the amendment for the IBC to seek guidance from the RAC on specific concerns that arise during the review process. Previously, the referral of protocols for public RAC reviews served this purpose for the numerous institutions whose research calls for registered IBCs. The absence of the RAC's involvement in clinical research oversight is already being observed, restricting access to pertinent expertise not widely available, prior to completion of public review and official

Many IBCs, excluding the long-standing academic medical centers traditionally at the forefront of gene therapy, lack the expertise to adequately conduct a risk assessment for clinical research as applied in pharmacy and clinical settings; and conversely, risk assessments and research oversight in clinics and hospitals differ vastly from the application of the NIH Guidelines and biosafety principles seen in the conduct of relevant pre-clinical research. According to the NIH Office of Science Policy (OSP, 26 August 2018), the last 10 years has seen a 59% increase in IBC registrations, which illustrates the rapid growth of this exciting clinical application. The majority of these IBCs are for locations which review HGT clinical research. For many locations, pharmacy and clinical staff have little to no experience in biosafety/biosurety and view the handling of HGT

products akin to chemotherapy. The safe conduct of HGT trials requires appropriate risk assessments and significant education, particularly pertaining to the replication competent biologicals being utilized. Research test articles and technologies applied to human subjects retain the risks specific to the material involved, and potential risks are increasingly being reported (e.g., CAR-T cytokine release syndrome, additional CRISPR off-target effects, and significant genomic damage following CRISPR-Cas9 nucleic acid break repair). The expertise of the RAC is clearly needed to provide far-reaching support for the safe research of these emerging and

Justification for eliminating RAC review is drawn from comparing the oversight of HGT studies to other areas of clinical research; however, not all clinical research studies pose the same types of risk. Similarly, not all oversight bodies share the same focus on research. All layers of oversight protect different portions of a 360° view of clinical research and each have their importance. Review by one body such as the RAC for ethical, scientific, and risk assessment of HGT research is outside the FDA purview, and would remain beneficial. Removing redundancy in research protocol processes is a good goal, but should not be done at the expense of reducing safety. Returning the mission of the RAC to its original purpose, belies the progress and refinement of the RAC duties to meet needs later identified. Returning

Biosafety professionals generally support and embrace the spirit of the proposed amendment to the NIH Guidelines to further streamline the processes for research oversight for HGT clinical trials. The efficiencies gained in removing duplicative steps decreases the research burden and may clarify for investigators the focus of oversight bodies involved in reviewing HGT clinical applications. Removing the requirement to complete Appendix M, allows for less redundancy and confusion between the IBC and the IRB. The documents required under Appendix M have been very helpful for IBC review, pulling out information on the study drug, personnel involvement, and trial logistics. Obtaining the pertinent information is still valuable for biosafety review and identification of containment and training needs. Conversion of Appendix M to a guidance document with significant

Please review the additional comments provided in the attached Excel table. Observations fall into general comments and those pertinent to specific proposed text. Issues include, but are not limited to: gaps in oversight that

	arise with the proposed amendment, additional RAC concerns, proposals, and errors/omissions in the proposed text.ABSA International appreciates the opportunity to review the proposed amendment to the NIH Guidelines. The comments provided are respectfully offered for your consideration. Please contact me with any questions or to request clarification. Respectfully, Hallie Hoskins, RBP, CBSP Biological Safety Officer University of Oregon
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	- - -

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Document:	Document Citation/Number: 83 FR 41082
"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)"	https://www.federalregister.gov/documents/2018/08/17/2018-17760/national-institutes-of-health-nih-office-of-science-policy-osp-recombinant-or-synthetic-nucleic-acid
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Table 1: General Comments

Observation/Concern	*Comment*	*Proposed change*
There is a gap in oversight of human gene transfer clinical studies under the current proposal.	Registration of Phase 1 studies is not mandatory on ClinicalTrials.gov as these studies do not meet the definition of an applicable clinical trial (ACT) as defined in section 402(j) of the PHS Act. ClinicalTrials.gov does not provide an adequate measure of oversight or transparency as clinical trial registration is not required until 21 days after enrolling the first human subject.	Maintain RAC for review of Phase I trials that meet the current criteria
A loophole exists in oversight of human gene transfer clinical studies under the current proposal.	Under FDAAA 801, the manufacture of a drug, biological, or device product in the US renders the study to be an ACT. A drug or biological product manufactured outside the US could be used and would not fall under FDAAA 801.	Expand scope of FDAAA 801 to include products manufactured outside of the US
Reducing duplications in submissions to the FDA and NIH could be met following a process similar to that in the European Union (EU) where registration of clinical trials are harmonized among multiple interests.	Use of FDA forms for both NIH and FDA purposes. FDAAA801 will need to be updated to reflect any changes to NIH Guidelines	Maintain registering with NIH but allow for the use of FDA forms; expand scope of FDA forms to include risk assessment questions similar to EU registering requirements

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Proposed RAC focus to emerging technologies will miss newly identified risks that impact current research	Proposed text shifts the focus of the RAC to emerging biotechnologies only; it is not stated to continue review of current research protocols in the new system. Example concerns: (1) Existing biotechnology (e.g. CRISPR/Cas 9) are now being used in humans without knowledge of off-target impact; (2) Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements (Kosicki, 2018)	Maintain, and potentially increase, RAC focus to continue evaluating risks in research involving existing and emerging biotechnology
Proposed changes may lead to dissolution of the RAC, and remove a national resource for research.	Removal of the RAC from the Guidelines, in conjunction with a 2-year revolving charter may lead to the dissolution of the committee even with its authorization in the Public Health Service Act. RAC charter will need to be updated for revised role and include recommended and responsive changes for continued role in research oversight.	Propose changes to the RAC charter and oversight be made that are responsive to stated concerns; that the NIH Director solicit input from impacted and involved parties; and that the draft charter and oversight be released to the public for review and comment.
What is the mechanism by which the NIH Director can solicit advice from the RAC? What is the mechanism for the IBC?	Inclusion of the process for soliciting input from the RAC on research protocols provide assurance to principal investigators and research entities of review by multiple world-class experts in their field. Transparency in this process for soliciting RAC input will continue to promote research rigor in study design and safety for all persons involved.	Do not eliminate every mention of the RAC from the Guidelines; maintain the RAC for Phase I and first in human research.
There is the potential that not all local IBCs and IRBs have the knowledge to address all the unknowns present.	The rapid growth of research involving nucleic acids and the conduct of human gene transfer studies outpaces the expertise available for service on IBCs. Few, if any, institutions would have IBC members with technical expertise at the level of members of the RAC.	Maintain registration with the NIH for review of projects of recombinant nature to ensure experts in this field have one central clearing house; clinicaltrials.gov is a central database but does not offer the same transparency for IBCs.

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There needs to be an option/requirement for Major Action, including HGT, to ensure applicable research goes back to NIH OSP for RAC review.	The criteria from the 2016 amendment should be added as to when the study would benefit from RAC review.	Include "New technologies; use of new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk; study relies on preclinical safety data that were obtained using a new preclinical model of unknown and unconfirmed value; or the proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate protocol rigorously;" as text to identify research areas subject to RAC review.
Appendix M has aided in assessing biosafety risks, identifying opportunities for mitigation, and determing training needs. Appendix M may serve a useful role even if deleted from the NIH Guidelines.	The IBC will continue to focus on worker safety with removal of Appendix M, and conduct thorough site-specific reviews as conducted for other protocols. The use of Appendix M has provided important details for the risk assessment of clinical research, including the observation that pharmacy and clinical staff have little to no experience on biosafety, disinfection, personal protective equipment, and engineering controls. The significant need for substantial training is commonly observed for the safe conduct of clinical trials.	Propose Appendix M be converted to a guidance document following revision.

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Table 2: Specific Comments				
Section Name or #	***Paragraph or #***	***Text at issue***	***Proposed change***	***Comment***
SUPPLEMENTARY INFORMATION	Paragraph 1	"Oversight mechanisms for ensuring HGT proceeds safely" are stated to "have sufficiently evolved to keep pace with new discoveries in this field." How was the sufficiency determined?	Define and describe "sufficient oversight". Include argument and references to support the characterization as sufficient oversight.	HGT clinical research differs from other clinical research. It is a relatively new field and oversight should continue to have unique mechanisms as clinical research proceeds. There is some precedent as clinical research involving radioactive materials as a research component should include radiation safety oversight.
	Paragraph 2	The purpose for the duplicative protocol processes for NIH are attributed to provide a forum for open dialogue and transparency. This stated purpose does not include the oversight for biosafety.	Explicitly state how biosafety will be maintained for HGT clinical research studies under these changes.	Omission of biosafety, as a purpose included in the NIH oversight to protect the research worker, the public, and the environment, is misleading with regard to priorities.
	Paragraph 3	The 2014 Institute of Medicine of the National Academies report, *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee* , is dated.	Maintain the RAC to review research (including clinical research) that merits review. This should be defined to include clinical research involving emerging technologies and research impacted by recent scientific findings.	The recommendations for oversight of rapidly emerging technologies that are now moving into clinical research may no longer be appropriate.
	Paragraph 6	Paragraph states that IBC safety reporting is complete once last participant is administered the final dose of the product.	Include longer reporting time frame; adverse events may not be immediately foreseen.	Reporting should include the proposed study time for follow-up and not the last dosing.

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Section Name or #	*Paragraph or #*	*Text at issue*	*Proposed change*	*Comment*
	Paragraph 6	With the proposed elimination of the requirements for safety reporting under Appendix M, IBC oversight should be completed immediately after the last participant is administered the final dose of product. Additionally, the role of IBC review is proposed to be amended to be consistent with FDA's current guidance regarding individual patient expanded access to investigational drugs. In this way, the role of the IBCs will be focused on providing local biosafety oversight of basic and clinical research involving recombinant or synthetic nucleic acids.	Clarify the specific application of the safety reporting under the context of clinical trial progression. Clarify also the integration of the amendment wih the FDA guidance cited, and provide the link to the specific guidance document.	Please clarify: the proposed requirement of IBC oversight seems redundant to 21 CFR 312.21 Phases of an investigation (b) and also 21 CFR 312.32 IND safety reporting.
	Paragraph 6	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.	Clarification is needed regarding expectations of the IBCs.	

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Section Name or #	*Paragraph or #*	*Text at issue*	*Proposed change*	*Comment*
Section I-A-1-a	Paragraph 1	The new wording removes the statement "Institutional Review Board (IRB) approval has been obtained."	Keep the wording in paragraph 1 stating "Institutional Review Board (IRB) approval has been obtained."	De-linking IRB approval and IBC approval, and the clinical trial from the experiment (introduction of rsNA into an organism), could lead to progression of clinical trial up to the point of injection and pose an undue burden on an IBC to approve research following already expended funds and human subject enrollment.
Section I-A-a-1	First sentence	Proposed test states to refer to Section I-E-7 for the definition of initiation; Section I-E-7 is proposed to be eliminated.	Correct proposed text to refer to Section I-E-4 as amended.	Corrected text: "no human gene transfer experiment shall be initiated (see "definition of initiation in Section I-E-4) until Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained;"
Section III-A		No provision remains with complete removal of RAC for Major/Minor Actions.	Replace the requirement for RAC review with potential for RAC consideration.	
Section III	Paragraph 1, (iii)	The revised wording removes "Institutional Review Board Approvals"	Keep the wording regarding "Institutional Review Board Approvals".	Recommend not siloing the IBC and IRB. Communication should be encouraged to promote an overall culture of safety.
Section III-C	Title			
Section III-C-1	Paragraph 5	The revised wording removes the statement "Institutional Review Board (IRB) approval has been obtained."		

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Section Name or #	*Paragraph or #*	*Text at issue*	*Proposed change*	*Comment*
Section III-C-1	Paragraph 3 (revised)	Definition of Individual patient expanded access IND is missing.	Include definition and justification as to why this research should be exempt under the *NIH Guideline.*	Evaluation needed (by the RAC) to determine if research under this category is not pertinent to the NIH Guidelines. Processes for this specific research category could be modified to avoid any negative impact to treatment; such as in modifying FDA form for biosafety oversight and RAC review.
Section III-C-1	Several paragraphs	Removal of several paragraphs after the definition of HGT. One paragraph has the language from the 2016 amendment including initial site and the IBC obligation to request RAC review.	OSP needs to clarify whether initial site review by IBC/IRB is required for HGT studies.	
Section IV-B-2-b-(1)	(vii)	Reporting of serious adverse effects to OSP during studies involving recombinant or synthetic nucleic acids.	(vii) seems to be removed and includes adverse events reporting- if removed, the functions of the IBC need to be clearly stated that it will not be responsible for reporting SAEs.	Incident reports should continue to NIH, via the the RAC, and not just the OSP. Not enough is known to stop adverse reporting as practiced under the 2016 *NIH Guidelines* .
Section IV-B-2-b-(1)	(iii)	These sections remove all references to Appendix M, but Appendix M can be converted to a useful tool for investigators.	Suggest keeping reference to Appendix M, but amending Appendix M to be guidance document for IBC submission of HGT protocols.	While Appendix M is removed under the proposed amendment, the required documents have provided key information for IBC review. Appendix M should be amended to make that needed information clear to the investigator and easy to find for the reviewer.
Section IV-B-6	(ii)			
Section IV-B-7	Paragraph 1			

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Section Name or #	*Paragraph or #*	*Text at issue*	*Proposed change*	*Comment*
Section IV-B-7-e(5)		This section refers to reporting requirements for HGT protocols in compliance with the *NIH Guidelines* as stated in Appendix M.	Reporting requirements should remain in place, but revised to exclude RAC reporting to match the proposed amendment, or amended to meet revised requirements of the RAC should it be retained.	Incidents, exposures, or serious adverse events should still be reported to NIH. NIH OSP should be made aware of any SAE involving rDNA in a trial.
IV-C-1; IV-C-3		Information in these sections refer to OSP as strictly administrative.	Create section within OSP or functioning alongside that is able to provide the scientific and ethical review.	Recommend clarifying earlier in the NIH Guidelines who will be conducting the scientific and ethical reviews and the required qualifications.
IV-C-2		Entire section	Recommend retaining the RAC and revising description to meet outcome desired.	Retaining the RAC is recommended by biosafety professionals. Revision of this section and the RAC Charter to describe the RAC agenda and process for solicitation is needed.
IV-C-3-a		Gene editing for HGT does not appear to be considered for review.	Maintain RAC at a minimum for gene editing HGT.	Refer to entire comments submitted for additional research fields to be covered by the RAC.
Section V	Paragraph V-B	Recommend adding clarification for investigator designation of exempt research.	Add: “Research identified as exempt by a PI should be reviewed by the BSO and/or the IBC for accurate identification under Section III.”	Added text will clarify the expected oversight for exempt designation for the PI.

Submission #39

Name:	Jason Keaton
Organization:	
Email:	(b)(6) - Personal Info @gmail.com
Comment:	Dear NIH, I am writing to support the proposed changes which would streamline the process to review gene therapy trials and to thank you for your efforts to create a more efficient government. As a private citizen and taxpayer, I was happy to learn of the elimination of redundant efforts between two organizations which both reside in the Department of Health and Human Services (i.e., NIH and FDA). Too often our government is lambasted for being inefficient; examples like this effort should be broadly communicated so that taxpayers can understand that the NIH and FDA work together to be more efficient and to save taxpayer dollars. Moreover, I was happy to hear that this efficiency will facilitate the development of life-saving therapies. Human gene therapy holds a lot of promise for the future of medicine, and we need to ensure as a society that oversight agencies are able to efficiently operate to support human gene therapy clinical trials (which are likely to be greatly increasing in number). In summary, I am supporting the changes because: • Facilitation of the development of life-saving technologies, and • Elimination of redundancies between two DHHS agencies demonstrates good stewardship of tax dollars Thank you for providing me this opportunity to comment in support of the proposed changes. Sincerely, Jason M Keaton 3384 S Princeton Avenue Milwaukee, WI 53215

Submission #40

Date	10/23/2018
Name:	Dr. Estuardo Aguilar-Cordova
Organization:	Advantagene, Inc.
Email:	eaguilar@advantagene.com
Comment:	Please see attached.
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/Public_comments_advantagene.pdf

Should Gene Therapy Trials be Considered for Exceptional Review?

We, and many in the gene therapy community, applaud the efforts of the NIH and FDA to reduce the regulatory burden for gene therapy products that have now entered the mainstream of biologic drugs. In addition to the three approved gene therapy products mentioned in the recent NEJM article (Collins, F.S. and Gottlieb, S., 2018), there is also talimogene laherparepvec (Imlygic, Amgen, Inc.), a recombinant viral immunotherapy product that was approved for melanoma in 2015. Many similar products for various cancer indications are in late stage, multicenter clinical trials. Even with the proposed changes to IBC reporting, access to those clinical trials is still negatively impacted by the NIH requirements, which are uniquely required for recombinant DNA products.

While the changes proposed are a welcome advance, they do not significantly impact the extraordinary burden for late stage trials that include gene therapy components. Eliminating the need for the initial site to determine if RAC review is required only significantly impacts early stage (Phase 1) single site studies. As reported in the article, RAC review was only required for 3 of 275 protocols since 2016. For most viral-based cancer products, RAC meeting review has not been required for more than 15 years. Eliminating the need to submit NIH reports that are already reviewed by the FDA will significantly reduce redundant government agency review efforts. However since initial Institutional Biosafety Committee (IBC) review must still be conducted at *each* location where the drug is administered, the highest unique burden for expanding clinical sites is not changed. Consequently, patient access to these potentially important new drug candidates, will not be significantly decrease by the proposed changes. Requiring IBC review is a particularly strong impediment for establishing multi-site trials and may provide no additional protection to patients, communities or NIH as drugs reach these later stages of development.

The IBC requirements for gene therapy studies were established 30 years ago, when the field was just beginning, and most everything about gene transfer in humans was an unknown. Patients and the NIH were best served by caution and public discourse. Today, after hundreds of trials, tens of thousands of patient doses of experience, and even approved gene therapy drugs that can be used anywhere without extraordinary review or conditions, those IBC requirements from so long ago may no longer be beneficial, yet come at significant costs, cause delays of up to a year or more at each clinical study site, and even preclude some sites from participating at all. For example, some community and army hospitals that do not do basic research, but have large patient populations, are hindered from participating because they do not have an existing IBC. These once-critical IBC review requirements may be harming patient interests. They must evolve or be completely eliminated to keep up with the advancements in scientific and clinical knowledge for gene therapy.

Institutional Biosafety Committees serve an important function in reviewing laboratory research for potential risk to staff, research animals and the environment from recombinant DNA and infectious agents in proposed research projects. Just like the Institutional Review Boards serve an important role in protecting human subjects participating in clinical trials. The IBC

concerns in clinical trials, however, are only particularly pertinent if the biologic or application is novel and may have unforeseen staff or environmental risks, which is not usually the case for agents in late stage clinical trials. Yet, current IBC requirements apply to all gene therapy trials that are conducted at even one institution that receives NIH funding. These requirements apply even if the biosafety concerns are no greater than those that one may have for a viral vaccine being administered in a local pharmacy, or, as for herpes-viral vectors for cancer, if a product of the same class is already available in the open market.

The exceptional requirement for IBC review disproportionately hinders progress in gene therapy development and particularly disadvantages participation in these trials by patients treated at community or private clinical practices, yet provide little to no added protection. IBCs are not simple to establish and are common in large research institutions, but almost non-existent in non-research clinical hospitals or independent clinical practices. While IBCs are charged with reviewing a clinical protocol for biosafety concerns, the current guidelines also require them to review the clinical protocol itself, the informed consent form, and any procedures for handling the biologic agent. These items are also the purview of multiple other committees, including the IRBs. Thus, even in institutions with established IBCs, most questions that arise from gene therapy clinical trial reviews are redundant with the IRB, pharmacy, and scientific review committees.

IBC review requirements significantly delay gene therapy research and inhibit patient participation. In some sites, IRB review cannot commence until after IBC review is completed, further delaying the initiation process. The IBC process is not familiar to most clinical coordinators and even at institutions with an established IBC, the process takes 4-12 months to complete. For institutions that do not have an IBC, a local committee must first be established. This step requires the institution to learn the requirements and establish written procedures for the committee. Then, the institution must form the committee and register it with the NIH. These requires identifying five members, two of which need to be “local” and non-affiliated, submitting their CVs to the NIH and waiting 4-5 weeks to see if they are approved. Since there is no established rule for what qualifies a member as “local” (there are no established distance or geographic rules) and because these two local members must also be unaffiliated with the institution, finding qualified members can be a significant challenge that sometimes takes several rounds of finding potential members, submitting to the NIH and waiting for their determination if the members are acceptable. As a result, this step alone can take 2-6 months or more. Once approved, the members must be trained for serving on an IBC, review the specific protocol documents, convene a meeting, vote, write and approve the minutes and finally generate an approval letter. IBC requirements consistently delay protocol approval by 6-12 months.

Having trials available at more institutions is an important factor to improve participation, especially for working families where travel to distant sites is not feasible and insurance companies may not pay for care outside their network. For precision medicine and gene therapy approaches that often target rare patient populations, trials need to be open at many more locations or need to be opened once a patient is identified. For more common diseases,

improved participation is critical to outcome improvement. Less than 5% of adults in the U.S. with cancer participate in clinical trials, and yet 70% express an interest in participating. An estimated 25% of cancer trials are never completed with the most common reason being poor accrual. The 2018 NIH single IRB policy for multi-site research is an encouraging step in making improved clinical trial participation and completion feasible. However, for gene therapy products, local IBC review is a significant hurdle that negates the improved efficiency of a single IRB and limits patients' access to new agents and consequently delays trial completion.

So, how do we move forward while still protecting the public? One option would be to eliminate IBC review for certain classes of products, especially once Phase 1 has been completed without biosafety concerns. This decision should be made at a central level to avoid redundancy and inefficiency. Certain classes of products may be exempted in-toto, as was the case for viral vaccines for infectious diseases. For example, replication defective and other common viral cancer immunotherapies delivered into a tumor may form such a class, since it is hard to imagine how multiple local reviews could further mitigate the risk to staff or the environment. The biosafety risk is higher for some live viral vaccines and blood products, yet they do not require IBC oversight. Moreover, local IBC members are not required to, and often do not have the expertise to make this decision. Identification of current products or classes of products that may be immediately exempted could be determined by the NIH Director to avoid any further delays. Going forward, this determination could be a function for the NIH RAC.

Submission #41

Date	10/23/2018
Name:	Abigail Stein
Organization:	Government and Community Relations
Email:	abstein@mcw.edu
Comment:	Good morning, On behalf of Kathryn Kuhn, please find the Medical College of Wisconsin's letter attached and copied below, supporting the proposed changes to the NIH Guidelines relating to Human Gene Transfer (HGT) clinical trials (83 FR 41082). Thank you, Abigail Stein, MBA Administrative Associate Government and Community Relations Medical College of Wisconsin
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/Response_to_83_FR_41082_MCW.pdf

MEDICAL
COLLEGE
OF WISCONSIN

Office of Government and
Community Relations

October 16, 2018

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

RE: 83 FR 41082 "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)"

Dear NIH Director,

We are writing in support the proposed changes to the NIH Guidelines relating to Human Gene Transfer (HGT) clinical trials.

At any given time, the Medical College of Wisconsin participates in over a dozen HGT clinical trials, as both initial and additional trial sites. Therefore, we have extensive experience with every aspect or administratively managing the Institutional £3iosafety Commillce ((IBC) review process for Section 111-C and Appendix M of the NIH Guidelines (which are both affected by the proposed changes).

We perceive the proposed changes to the NIH Guidelines to be positive, eliminating several redundancies which are burdensome to manage at our institution, while also maintaining critical safety protocols for research participants. The following are examples of activities which were redundant, and which will continue to be handled by more appropriate committees/ federal agencies: Monitoring human research participant welfare will continue to be a function of an organization's Institutional Review Board (IR13). The IRB is the most capable committee to monitor human research participant welfare and eliminating the duplicative requirement for IBC's to also carry out this function will reduce unnecessary redundancy.

- Reporting on Serious Adverse Events (SAE) will continue to be required functions of the principal investigators and the IRB. There arc currently processes in place for reporting S/\Es to the FDA, through the !RB. The fDA is well-suited to monitor clinical trials in which they have approved to be conducted, and, as a result, duplicative reports do not add value to the fD/\·s safety monitoring process.
- Submission of annual repo11s will continue to be submitted to the FD/\ via the IRB and Pl's. Removing the IBC and NIH from this process allows the FD/\ (a more appropriate agency) to be responsible for monitoring human research participants welfare during active clinical trials.

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These changes will allO\v the IBC to have a greater focus on what we are best capable to do: assessing how to safely conduct biological research and prevent the exposure of research materials to the personnel conducting research, the community, and our environment.

The proposed changes to the NIH Guidelines will not create any gap in our ability to safely assess the risks associated with HGT clinical trials, for example:

- The agents which are used in HGT clinical trials are similar to the agents which are commonly used in non-HGT basic science research that our IBC routinely reviews for biosafety, for example:
    - Viral vectors are routinely administered to live animals and cell culture
        - Notably, the vast majority of these viral vectors are much more hazardous than the viral vectors used in HGT clinical trials
        - Administration to animals typically involves introducing the agent via the use of a needle; while the vast majority of HGT trials arc restricted to safer administration systems

In summary, at the Medical College of Wisconsin, the proposed changes to the NIH Guidelines will facilitate a more efficient review ofHGT clinical trials by eliminating redundant processes and allowing the lBC to review HGT clinical trials in exactly the same manner in which we review more hazardous non-HGT basic science research.

Thank you for the opportunity to comment on the proposed changes to the NIH Guidelines, and thank you for being mindful of the burden to institutions participating in HGT clinical trials and eliminating redundant administrative processes.

Best regards,

Kathryn Kuhn
Vice President
Govern111ent and Co1111111111ity Relotio!ls
Medical College of Wisconsin

Submission #42

Date	10/23/2018
Name:	Jacqueline Hoats Shields
Organization:	University of Michigan Office of Research (UMOR)
Email:	jhoats@med.umich.edu
Comment:	Please find, attached, comments from the University of Michigan IBC on the proposed changes to the NIH Guidelines regarding review of human gene transfer trials. Sincerely, Jacqueline Hoats Shields Associate Director, Research Safety Compliance University of Michigan Office of Research (UMOR)
Upload Attachment (file extensions accepted: PDF, XLS, XLSX, DOC, DOCX):	https://osp.od.nih.gov/wp-content/uploads/rac-comment-form/uploads/Letter_from_Univ_Michigan_IBC_on_NIH_Guidelines_changes_2018.pdf

IBC INSTITUTIONAL BIOSAFETY COMMITTEE
UNIVERSITY OF MICHIGAN

October 22, 2018

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

RE: Proposed changes to the NIH Guidelines

Dear Dr. Tucker,

Members of the University of Michigan Institutional Biosafety Committee (IBC) experienced in review of human gene transfer clinical trials note that the removal from the NIH Guidelines of Appendix M in its entirety leaves the expectations of IBCs unclear in a number of areas:

- The removal of Appendix M in its entirety 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.

- Secondly, without mandatory adverse event monitoring it is unclear what the IBC is supposed to do to complete oversight at the end of the project. It seems that if the IBC is to complete its oversight "immediately after the last participant is administered the final dose of product," that this would entail at least some review of the adverse events that have accumulated during the trial.

- Further, IBC review of the informed consent is still valuable to make sure that it covers potential IBC-related issues that the IRB may not recognize.

The guidance provided in Appendix M is a unique and valuable resource for investigators, sponsors, and reviewers of these studies. Moreover, if IBCs are to have a role in oversight of human gene transfer studies beyond the point of initial approval, then it must be clarified what types of reports (e.g., AEs) the IBC will receive during the study in order to complete that oversight function.

We appreciate the effort to streamline the review process for these studies. As you determine how to proceed we hope that you will carefully consider our input and that the next version of the NIH Guidelines will include clear guidance on the expectations 1) for investigators and sponsors regarding submission criteria, and 2) for IBCs on their review and oversight functions during the conduct of human gene transfer clinical trials.

Sincerely,

Christiane E. Wobus, Ph.D.
Chair, Institutional Biosafety Committee
Associate Professor of Microbiology & Immunology
University of Michigan

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Submission #43

Date	10/24/2018
Name:	Barb Deichl
Organization:	
Email:	(b)(6) - Personal I n@ wi.rr.com
Comment:	Dear NIH, I am writing as a taxpayer and private citizen concerned about regulatory redundancy, and excessive costs of clinical research. I support the proposed changes to the NIH Guidelines relating to Human Gene Transfer (HGT) clinical trials. The changes eliminate several redundancies, which can be expensive to manage, and don't enhance safety for the research trial. Several redundancies eliminated by removing Appendix M include: - Removing the requirement for an IBC to monitor and report on the welfare of the research participant. This is already coordinated, monitored, and reported by an IRB, so it is duplicative. - Serious Adverse Events (SAEs) will continue to be reported by Principal Investigators (PIs) and an IRB; ending the requirement for duplicative reports from the IBC. An IBC reporting function does not enhance safety, and only complicates the administrative process and adds administrative burden to the institution performing the trial. - Annual reports are submitted to the FDA by the IRB and PIs. Removing the IBC and NIH from this process allows the FDA to continue their responsibility for monitoring the welfare of research participants; again removing redundancy that doesn't add value. The proposed changes to the NIH Guidelines will alleviate redundancies, allowing entities best suited for monitoring patient welfare (i.e. FDA) to continue, and allow an IBC to continue reviewing the HGT clinical trials in the same way non-clinical basic science research is conducted. Thank you for this opportunity to comment. These changes work toward removing redundancies in the regulatory arena, reducing the burden to institutions, and lowering costs to taxpayers as therapies are brought to market. This effort also demonstrates the ability of NIH and FDA to work together, reducing government inefficiencies and saving taxpayer dollars. Sincerely, Rebecca Seevers