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IOM RAC Workshop Panelist Comments

We present here a selection of written comments that were submitted by panelists who spoke at the IOM RAC workshop on August 6, 2013.

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I AM SPEAKING AS AN investigator who has served as principal investigator or IND sponsor on over 20 gene transfer studies since 1993. I also served on the NIH committee chaired by Inder Verma that reviewed the RAC in 1995 and served as a member of the RAC from 2004 to 2007.

In the early years of gene therapy the RAC served a crucial function in allowing public review and discussion of this new therapeutic approach. With 20 years of experience in the field though, I believe that review of every new study is no longer needed. A gene transfer protocol at my institution will currently receive internal review by our NCI cancer center protocol review committee, the IRB and the IBC, and external review by the RAC and the FDA. The requirement to submit a full response to Appendix M for RAC review is an additional burden on investigators when the protocol will already receive a comprehensive safety review from the FDA. If the protocol is selected for public review the investigators have a further delay and have to identify funds for a trip to Washington for 2–4 team members. I would therefore endorse the recommendation from the committee convened by the American Society for Gene and Cell Therapy in 2012, which concluded that ''The RAC would terminate review of individual clinical protocols and would instead identify new areas of research that require a public forum for discussion and review.''

In my opinion one of the major contributions of the RAC over the past decade has been in communicating events in gene therapy trials to the broad community in a timely manner at either their quarterly meeting or in special conferences. Examples include conferences about the cases of T cell lymphoproliferation that developed in patients receiving genetically modified stem cells to treat gamma chain SCID and, more recently, conferences about strategies to mitigate toxicity, seen in some studies with T cells genetically modified with chimeric antigen receptors while preserving the beneficial anti-tumor effects that have been observed. There are also several cases in which public review of SAEs at RAC meetings has been highly beneficial to the field. Examples would include discussion of adverse off-target effects seen in studies using codon-optimized TCRs. This is a unique function of the RAC, as SAEs submitted to the FDA are confidential. The RAC also has the ability through the GEMCRIS database to identify AEs in similar types of trials and present this publication publically to inform investigators, which is a significant benefit to individual investigators and the field.

I would therefore suggest that the current process for submission of a new protocol to the RAC be modified to a simple registration system to allow follow-up reports in GEMCRIS rather than submission of the full Appendix M. I would recommend that the role of the RAC be modified to focus on public policy conferences and that they continue to provide the crucial role of providing a venue for public discussion of SAEs and other issues in ongoing trials.

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Background

My research focuses upon translating basic cell and gene transfer strategies into first-in-human trials. Over the past 17 years, I have been the regulatory sponsor for approximately 50 INDs and appeared before the NIH Recombinant DNA Advisory Committee on numerous occasions. In collaboration with the biotechnology industry my laboratory conducted the first trials using lentiviral vectors (0107-488) and, most recently, zinc finger nucleases (0704-843) and mRNA electroporated T cells (1010-1072). My group conducted the first chimeric antigen receptor (CAR) trials in the late 1990s,[1,2] and recently this technology has advanced and now shows prominent efficacy in advanced leukemia in adults and children.[3–5] By way of disclosure, this technology was recently licensed by Novartis, and international trials with CAR T cells for leukemia are anticipated to begin in 2014. In addition, I am an active member in the American Society of Gene and Cell Therapy.

While conducting many trials involving gene transfer with engineered T cells, my group has encountered several unexpected severe adverse events (SAEs). Most prominently these have been anaphylaxis following infusion of mRNA electroporated T cells[6] and death from cardiac toxicity due to engineered T cells.[7] The unexpected cardiac toxicity was the first example of off-target toxicity from genetically engineered T cell receptors. The trial was subjected to public review by OBA/RAC in September 2010 (http://oba.od.nih.gov/oba/RAC/meetings/Sept2010/RAC_Minutes_09-10.pdf). We presented the initial results of our investigation of the SAE to the OBA/RAC on June 19, 2012 (http://oba.od.nih.gov/oba/RAC/meetings/June2012/1_TCRUpdate_June.pdf), and subsequent investigation has shown that the engineered T cell receptor bound to titin,[8] a protein expressed in striated muscle tissue, resulting in lethal cardiac toxicity. A lesson learned from this unfortunate event was that the available preclinical models did not uncover this unexpected toxicity.

State of Gene Transfer Research

When the RAC was created 40 years ago, the risks of recombinant DNA technology were not well understood scientifically, and the public had generalized concerns. Over the years, advances in basic science coupled with clinical experience have demonstrated that gene transfer is no more risky than other new therapies. The experience gleaned from a wide range of gene therapy protocols in the United States, and Europe has not substantiated concerns for alteration of the human germ line or generation of new novel pathogens. Furthermore, cytotoxic chemotherapy has been shown to have more frequent SAEs (e.g., secondary leukemia and myelodysplastic syndromes) than gene transfer protocols. This is relevant, since historically more than 70% of gene transfer protocols have been for cancer. Yet new chemotherapy protocols are not subject to OBA/RAC oversight.

Gene transfer technology is now a maturing field. This is perhaps best exemplified by the recent decision of nearly all large pharmaceutical companies to commercially advance gene transfer strategies. Multiple late-stage clinical trials for FDA registration are now underway. For example, at my institution, a phase III trial for Leber congenital amaurosis is expected to result in FDA approval (0910-1005). Numerous other approaches currently in the clinic will likely lead to FDA approval in the fields as diverse as cancer, congenital disorders, and chronic infection during this decade. However, at this point, there are no FDA-approved gene transfer therapies in the United States; yet, there are in Europe (Glybera for lipoprotein lipase deficiency) and in China (Gendicine for head and neck cancer).

Gene Transfer Oversight

Initially, nearly all gene transfer research in the United States was sponsored by the NIH. However, at present, the RAC has oversight only over NIH-funded gene transfer research. Based on the recent entry of industry into this field, this implies that an increasing proportion of research (i.e., pharma and biotech in the United States and all European and Asian protocols) will not be subjected to RAC protocol review.

Another more recent development is the advent of the clinicaltrials.gov website. All trials in the United States, whether academic or industry sponsored, are required to register here. Thus, GeMCRIS, while an elegant website, is no longer comprehensive.

In addition to the above, major changes in the NIH have occurred that can have an impact on gene transfer oversight. The emergence of the Clinical and Translational Science Award (CTSA) program in 2006, and the subsequent incorporation of the CTSA into the National Center for Advancing Translational Sciences (NCATS) in December 2011, have the potential to further impact the mission of the OBA/RAC (for details see the IOM report on CTSA, June 25, 2013). The other major change at NIH since the RAC was established is the substantial reduction in financial resources that have occurred and are projected to occur at NIH.

Based on all of the above changes, I recommend that individual protocol review by OBA/RAC should be terminated, and that clinicaltrials.gov can subsume the previous ''mission critical'' functions of RAC protocol review and GeMCRIS.

All clinical research needs to have oversight. The oversight process should be transparent and present a level playing field, in that the oversight process should not be more burdensome for gene transfer research than for other fields. Furthermore, the regulatory burden should not be greater for academic trials than it is for industry-sponsored trials; at present, the regulatory burden is larger for NIH-sponsored trials since RAC oversight is not required for the latter.

Recommendations Going Forward

a) *Enhance the educational mission of RAC*. The major remaining mission of the RAC is to conduct public education on emerging forms of novel therapies such as iPSC and ES cells. This is best done at the federal level, as it reduces the real and perceived biases of the public by scientists and industry sponsors. I have had the personal experience of the lay public conflating our use of HIV-based lentiviral vectors with wild type and pathogenic forms of HIV; the misinformed report that we infected a child with HIV went viral, with more than 1 million views in a week.[9] An increasing need in the field of cell and gene therapy is type II translational research to educate the lay public and community physicians about the coming wave of cell and gene therapies that will be FDA approved.

b) *Eliminate individual protocol review by OBA/RAC*. This review is best done by FDA and IRBs, since both industry and NIH sponsored protocols are already subject to review by these health authorities that are empowered by federal regulations. This will restore equity for all forms of investigational therapeutic clinical research and will also enhance U.S. competitiveness (recall Glybera and Gendicine).

c) *Ease burdensome reporting requirements and harmonize safety reporting*. At present, academic investigators must report SAEs to IRB, FDA, RAC, IBC, DSMC, and other internal committees at their respective academic institutions. The reporting requirements are not harmonized (i.e., some agencies require reports in 3 days, while others in 7 days, using different formats); this is confusing and can create liabilities. The establishment of a sole central reporting

site should be considered, so that safety data can be automatically ported to the various agencies. This would increase protocol compliance and decrease the regulatory burden.

d) *Consider moving or incorporating OBA/RAC into NCATs*. This would result in more effective use of the reduced financial resources at NIH and could apply RAC expertise to all fields of clinical research.

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Overview

Most human subjects research (HSR) conducted in the United States is subject only to individual protocol review by an IRB with additional periodic review by the FDA where biomedical products are involved.* Gene transfer research (GTR), however, is required to undergo additional federal and local review. All research involving NIH funding must be registered with the RAC, and all such research *may* be subject to individual protocol review by the RAC.† In addition, such GTR must receive local approval by an institutional biosafety committee (IBC) in addition to IRB approval.‡

The United States has no consistent framework for providing oversight of emerging technologies. Additional oversight is more likely where the technology has been a subject of public controversy. Thus, GTR, which was a target of great public controversy at its emergence in the 1970s and 1980s, is subject to additional RAC and IBC review. Stem cell technologies are subject to an additional patchwork of NIH, state and local (SCRO) oversight. On the other hand, nanotechnology, which has thus far avoided much public controversy, is not subject to consistent additional oversight despite some recommendations

*Research that involves specific issues may be subject to additional federal oversight on an *ad hoc* basis (e.g., hazardous substances may be subject to EPA oversight), and state law may impose additional requirements for specific types of research (e.g., psychiatric research).

†The RAC's role now is advisory, so no RAC approval is required, but that does not eliminate registration and submission requirements nor, if applicable, protocol review. Preparation of those materials, even for those studies that do not have individual protocol review, can be time consuming and require documentation that may not have been required by the FDA or IRB.

‡NIH OBA has recently proposed streamlining IBC review by no longer requiring IBC review of clinical trials where the safety of the proposed dose of the gene transfer product has been established in comparable population. Federal Register /Vol. 78, No. 92 /Monday, May 13, 2013.

for such oversight.[§] Similarly, synthetic biology, which, although controversial, has also avoided becoming a lightning rod for public scrutiny, remains largely outside additional oversight except for research that fits under RAC guidelines.

There are reasons to treat GTR differently than most HSR. Gene regulation is not yet completely understood, novel biological entities are being created and released into humans, animal studies are incompletely predictive, and immune responses are often unpredictable. After more than three decades of GTR, no gene therapy product has been approved for sale. But there may be no reason to treat GTR differently than other emerging technologies. However, that may be a better argument for applying the GTR model to other emerging technologies rather than reducing the RAC's role in GTR. The oversight rubric for GTR is our longest running experiment with oversight of emerging biotechnology. And, despite serious problems like the Gelsinger incident and leukemia in SCID children, it has largely been a success. It has not remained static but has evolved over the forty years of the technology's existence. As product development nears approval, FDA's role has increased and the RAC's has diminished. The overall structure, where the RAC acts like a limited central IRB, makes much more sense than the fragmented system of state and local SCRO review under which much stem cell research is often regulated. There are complaints of additional burdens and delay, but delay is not necessarily a bad thing when it comes to emerging technologies. Like many systems of risk oversight, it may be easier to measure the burdens than the bad outcomes avoided. Those burdens may be better alleviated by a few administrative tweaks to make sure that protocols submitted for individual review merit that review rather than substantive changes to the existing structure.

IBC, IRB, and FDA Review

IBCs

There has been relatively little assessment of the role of IBCs in the context of GTR.** One of the early concerns leading to the creation of the RAC, IBCs and oversight guidelines for GTR was the potential for accidental release of dangerous organisms. Thus, the primary role of the local IBC is the review and monitoring of the study plan for the receipt, storage, handling, preparation, and administration of the experimental agent. By the 1980s, it was clear that most of the early fears were unfounded in the context of GTR. IBCs do play an important role in maintaining good laboratory practices in GTR. More substantively, IBC members may provide important scientific expertise for the IRB on the administration of the experimental agent and the safety concerns involving the vector and/or transgene. Nonetheless, since the death of Jesse Gelsinger in 1999, many institutions appoint an additional *ad hoc* scientific review committee to advise the IRB. That committee may or may not include IBC members.

To the extent there are general concerns about IBCs, they center on the added burden of an additional submission for regulatory oversight. The recent NIH proposal to streamline such requirements should, if finalized, considerably reduce that burden.

IRBs

While there has been more assessment of the role of IRBs in GTR than IBCs, there has still been relatively little systematic review of how IRBs function with GTR. This is consistent with the fact that there has been relatively little empirical study of IRBs in general. But almost certainly, many of the complaints about IRBs' performance are equally if not more applicable to GTR.[††] Most important, few IRBs will have sufficient scientific expertise required for scientific review of GTR. In addition, since IRBs are acutely aware that the Gelsinger case, one of the few instances of an IRB being subject to potential legal liability, involved GTR, IRBs (and their institutions) may be overly protective in the case of GTR without actually having the capability to accurately assess the real risks. This may result in delay or even inappropriate conditions or rejection. Better and more communication between IRBs and FDA and the RAC could limit delay and inappropriate conditions and may even allow institutions to forego *ad hoc* scientific review, thus speeding IRB approval.

The Gelsinger case does provide the most in-depth assessment of an IRB's (the University of Pennsylvania's) performance with GTR. Not surprisingly, that assessment was not positive. The IRB was found not to be sufficiently sensitive to issues of financial and institutional conflicts of interest and to have allowed the informed consent to understate or ignore risks while overstating benefits. In addition, the IRB failed to pay sufficient attention to related adverse events.[‡‡] Perhaps unfortunately, however, the existence of the conflicts of interests has largely eclipsed what may be the more important discussion: whether the IRB (indubitably one of the more sophisticated IRBs in the nation) had the ability to anticipate the risks that were realized in Gelsinger's death, or whether any amount of oversight could have precluded that outcome. A related and still unanswered question is whether greater RAC oversight (the Gelsinger case occurred after the RAC lost approval authority) would have made any difference.

While there has not been much systematic assessment of IRB actions with GTR, an NHGRI ELSI project called ''The Social Construction of Benefit in Gene Transfer

[§]Leili Fatahi, et al. ''Recommendations for Nanomedicine Human Subjects Research Oversight: An Evolutionary Approach for an Emerging Field,'' 40 J.L. Med. & Ethics 716 (2012). Research involving nano-vectors is subject to RAC review.

**Most recent review of IBCs' role has been in the context of select agents and dual use research; literature focusing on IBC's role in GTR is mostly dated from the 1980s.

[††]*See, e.g.,* President's Comm'n for the Study of Ethical Problems in Med. & Biomedical & Behavioral Research, *Implementing Human Research Regulations* 105–14 (1983); Ezekiel J. Emanuel et al., *Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals*, 141 Annals Internal Med. 282 (2004).

[‡‡]Robin Fretwell Wilson, *The Death of Jesse Gelsinger: New Evidence of the Influence of Money and Prestige in Human Research*, 36 Am. J.L. & Med. 295, 302–315 (2010).

Research''[§§] included interviews of forty-three IRB chairs and representatives.*** Those interviews revealed that even experienced IRBs had relatively little experience with GTR. Many of the IRB representatives indicated that they actively sought information from the RAC and FDA and investigators. But many of the representatives also exhibited limited understanding of the full oversight rubric for GTR and the authority of RAC review. Some IRBs were also unaware of Appendix M in the NIH guidelines and failed to consider that information in their review. This may have created conflicts between IRB documents and RAC recommendations for informed consent. Since that study, OBA has been actively engaged in education projects, but the overall success of that endeavor has not been assessed.

IRBs are ill-equipped to systematically respond to adverse event reports and may be even more so in the context of GTR. IRBs are aided in this effort by data safety monitoring boards (DSMBs) and the RAC's Gene Transfer Safety Assessment Board (GTSAB) functions as a ''national DSMB.''

Finally, IRBs are unlikely to learn much from each other. GTR does not represent a significant part of most IRBs' workload and is unlikely to be a focus for IRB education. IRB meetings and minutes are not public, so individual IRB protocol deliberations are not shared.

FDA

Throughout much of the early history of GTR, FDA's relationship with the RAC was more competitive than cooperative.[†††] The RAC role in the first decades was predominant. Most research was not yet at the clinical trial phase and the FDA did not have either the expertise or the regulatory authority in place to take an active role. The FDA claimed authority to regulate cell- and tissue-based products in 1983, and in 1993, the FDA announced that it would fully regulate somatic cell therapy products and gene therapy products.[‡‡‡] In 1995, the National Task Force on AIDS Drug Development identified dual FDA/RAC oversight as an obstacle to speedy development of AIDS treatments. By 1996, the FDA acquired full approval authority over gene therapy from the RAC and final guidance was issued in 1998.[§§§] The fact that the FDA regulates gene therapy products under an overlapping rubric with somatic cell therapy products may become an important advantage since there is increasing merging of the technologies.

Unlike IRB or IBC oversight of GTR, the FDA's oversight has been studied extensively, first during review of RAC authorities, then extensively after the Gelsinger incident (both in the scholarly literature and by Congress), and more recently as a potential model for other emerging technologies. There have even been some attempts at empirical albeit preliminary study.**** During the early years of FDA oversight, it was possible to argue that the FDA lacked full capacity for review of GTR. Staff expertise was limited and funding deficits made it difficult to remedy that shortfall. The advent of user fees and additional Congressional funding have largely erased that difficulty and most people would agree that the FDA has expert staff that has the additional advantage of full-time positions and broad experience with GTR—both as regulators and sometimes as researchers themselves. Moreover, since FDA approval is necessary to bring a product to market, there is evidence that researchers have been more careful to comply with FDA regulations than with RAC requirements. For example, in the late 1990s, researchers were far more assiduous about reporting adverse events to the FDA than they were to the RAC.

But FDA product review is quite different than that conducted by the RAC. First, FDA's scope of review is narrower. The FDA reviews products under statutory standards for safety and efficacy. That means that some ethical issues are outside FDA's authority. FDA tends to spend far less time considering consent issues than either local IRBs or the RAC. In addition, the scientific review is focused on whether the safety and efficacy metrics are met for a particular product; a broader view of the overall merit or direction of the science is unlikely. Second, FDA's review takes place as a dialog between the sponsor and the FDA. The meetings are entirely private and the substance of the meetings is never made public. Moreover, although FDA officials may know the details about a great deal of GTR research involving many sponsors, they are prohibited from revealing any specific details about another sponsor's product publicly or during their individual reviews of any other sponsor's product. This methodology is generally favored by commercial sponsors since it protects their intellectual property. And it is frequently argued that this enhances innovation because sponsors will only seek product approvals if their intellectual property is adequately protected. But it is certainly possible that broader scientific discussion might speed all GTR research and even more likely that public discussion makes safety issues more widely understood.[††††] Finally, even though recent legislation requires more information about FDA-regulated clinical trials to be made public,[‡‡‡‡] this reporting has limited detail and results may not be published until a product has been approved.

[§§]1 RO1 HG 02087-01, ELSI Program, National Human Genome Research Institute, NIH.

***Nancy King summarizes some of the findings of these interviews in Nancy M.P. King ''RAC Oversight of Gene Transfer Research: A Model Worth Extending?'' 30 J. L. Med. & Ethics 381, 384 (2002).

[†††]There are a number of full narratives of this history. See, e.g., Richard Merrill and Gail Javitt, ''Regulation of Gene Therapy by the U.S. Food and Drug Administration,'' in *Encyclopedia of Ethical, Legal, and Policy Issues in Biotechnology* (Thomas J. Murray and Maxwell J. Mehlman, eds.), John Wiley & Sons. (2000); J. M. Rainsbury, ''Biotechnology on the RAC: FDA/NIH Regulation of Human Gene Therapy,'' 55 *Food & Drug Law Journal* 575 (2000); Susan M. Wolf, Rishi Gupta, Peter Kohlhepp, ''Gene Therapy Oversight: Lessons For Nanobiotechnology'' 37 J.L. Med. & Ethics 659 (2009).

[‡‡‡]58 Fed. Reg. 53248. CBER sent the biotechnology industry non-binding advice on regulation of gene therapy techniques in 1991. CBER, Points to Consider in Human Somatic Cell and Gene Therapy [Draft] (Aug. 1991). and FDA has continued to issue separate guidance in this area.

[§§§]www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm072987.htm

****Wolf *et. al*, n. 10 *supra*.

[††††]NIH guidelines state that ''A human gene transfer experiment submitted to NIH OBA should not contain confidential commercial information or trade secrets, enabling all aspects of the review to be open to the public.'' Some sponsors would argue that submission of a protocol for any unapproved product involves commercial information.

[‡‡‡‡]FDAAA, Sec. 801; these requirements do not include Phase 1 studies.

Nonetheless, all evidence shows that the FDA regulates carefully and comprehensively in this area. The FDA guidance here may be more substantive than procedural and seeks to educate as well as regulate.[§§§§] And the FDA has not yet approved any human gene therapy product for sale.

How do other regulatory bodies interact with or supercede the RAC?

All of the other GTR oversight bodies, the FDA, local IRBs and IBCs, technically supercede RAC authority in that the RAC's role is advisory only. This means that where there is conflict, a local IRB's conditions on a protocol or consent trump the suggestions of the RAC. There is evidence of some confusion about these roles. Further education of IRBs may alleviate some of these problems; IRBs that understand the RACs role are more likely to use its advice consistently. Moreover, the RAC can play an important role in alleviating institutional wariness of GTR generally. In the aftermath of the Gelsinger incident, both the FDA and RAC pledged to operate more cooperatively, and by all accounts they have done so.*****

Are the roles or functions of IRB and IBC duplicative of the RAC?

One way to look at the relationship of the RAC to local IRBs and IBCs is as a limited ''central'' IRB or IBC. The RAC now reviews relatively few protocols, but in its role reviewing individual protocols there is the potential for duplication or even conflict with local bodies. Yet, with proper delineation of roles, that duplication is either eliminated or is an enhancement of oversight. In his statement to Congress in 2000, LeRoy Walters summarized the ethical role of the RAC as answering four questions:[†††††]

1. What are the potential harms and benefits of the research to the research subjects who will participate in a planned study?
2. 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?
3. 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.
4. How will the privacy of research subjects be protected and the confidentiality of their medical information preserved?

All of these questions are within the purview of IRB review. However, as noted previously, it is likely impossible for a local IRB to duplicate the level of expertise on the RAC, so the RAC may be better suited to answer many of those questions than the local IRB. IRBs need to learn how to use RAC advice to augment their expertise and speed up review. The HSR community is already engaged in a broader discussion about what the role of multisite central IRBs should be. The solutions generated there will likely be equally applicable to the RAC even though the RAC currently lacks approval authority.

Does individual protocol review by RAC enhance other layers of GTR oversight?

NIH guidelines state that such review may be (1) initiated by the NIH director or (2) initiated by the NIH OBA director following a recommendation to NIH OBA by (a) three or more RAC members or (b) a federal agency other than NIH.[‡‡‡‡‡] There have been complaints that this process is outdated, that nonexpert members flag inappropriate studies, and that ethical discussion dominates the review.[§§§§§] Ironically, that complaint may be evidence of success on the part of the RAC since IRBs consistently struggle to provide nonscientists and community members a real voice. Moreover, one of the central purposes of the RAC is to provide a public forum for ethical discussion. It is possible that the most appropriate protocols are not being reviewed, but there may be both scientific and nonscientific reasons for a protocol to be submitted for discussion. Moreover, even an erroneous belief that a study poses issues may provide valuable discussion if that viewpoint is widely shared, and discussion can shed light on the realities of the situation.

The RAC was created in part to assure the public that everything is being done to protect the public from the potential risks of technology. While the recent experience with GTR has been relatively safe, the assurance that extra oversight is in place may actually protect the technology should something unexpected occur. Given that no product has yet been approved, and there are still many scientific aspects that are not well understood, it is difficult to argue that the science is so mature that the burdens exceed the benefits of extra oversight—if that oversight is not conducted with a heavy hand. Presumably, as novel questions diminish, the number of protocols submitted for individual review should also diminish.

Finally, there is evidence that the more removed the advisory bodies are from the actual research taking place, the less impact they have. Individual protocol review allows RAC members and the public to have a first-hand understanding of the novel issues raised by GTR and provides a public discussion of real concrete problems.

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[§§§§]See, e.g., www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM359073.pdf

*****Both Dr. Corrigan-Curay and Dr. Takefman described significant and useful FDA-RAC cooperation; there is of course no need to repeat that here.

[†††††]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.

[‡‡‡‡‡]NIH Guidelines, Appendix M-I-B-2.

[§§§§§]Xandra Breakefield presentation to the IOM about the RAC, June 4, 2013.

Jeffrey D. Chulay

The *NIH Guidelines* apply only to research that is conducted at or sponsored by an institution that receives any support for recombinant or synthetic nucleic acid research from NIH, but individuals, corporations, and institutions not otherwise covered by the *NIH Guidelines* are encouraged to follow the standards and procedures set forth in Sections I through IV of the *NIH Guidelines*. Therefore, almost all corporations and institutions comply with the *NIH Guidelines*, either because they receive some funding from NIH or they agree to voluntary compliance.

I have worked for two small biotechnology companies that conduct gene transfer research. One of these (AlphaVax) uses a recombinant alphavirus vector to develop vaccine products. The other (AGTC) uses a recombinant adeno-associated virus (AAV) vector to develop products to treat inherited genetic defects. At both companies, the major activities required in order to comply with the *NIH Guidelines* have been the establishment of an institutional biosafety committee (IBC) and submission of documents to the NIH Office of Biotechnology Assessment (OBA) related to RAC review of clinical trial protocols.

Establishment and Operation of an IBC

At each company, I was responsible for organizing the establishment of an IBC to review and approve recombinant DNA research conducted at the institution. This required a total of approximately 120 person-hours of effort, including (1) 50 to 60 person-hours of my time to identify and recruit appropriate external IBC members and conduct training at the initial IBC meeting, (2) 20 to 30 person-hours of scientist time to develop registration documents for review by the IBC, and (3) 30 to 40 person-hours for registration document review and participation in the initial IBC meeting by the five IBC members.

At each company the original registration documents were comprehensive and the nature of the recombinant DNA research did not change. Therefore, the effort involved in ongoing operations of the IBC, consisting of an annual IBC meeting for review of registration documents and a biological safety officer report, has not been onerous.

RAC Review of Clinical Trial Protocols

At each company, we elected not to have clinical trial protocols reviewed by the company's IBC. The *NIH Guidelines* require that each clinical trial protocol be reviewed by the IBC at each participating site, and it was decided that no value would be added by undergoing review by another IBC.

Therefore, the activities required for review of clinical trial protocols are (1) preparation of Appendix M; (2) submission of Appendix M, the clinical protocol, and associated documents to OBA; (3) submission of the clinical protocol and Appendix M for IRB and IBC review at each site; (4) participating in RAC meetings if the protocol is selected for public review; and (5) submission of annual reports and occasional adverse event reports to OBA.

An individual who is familiar with the *NIH Guidelines*, the clinical trial protocol, and the methods used to produce the product to be used in the clinical trial can generate an Appendix M in 40 to 60 person-hours of effort. The other documents required for submission to OBA require little additional effort to prepare.

The IBC at each site expects to receive an Appendix M for each clinical trial protocol that they review, and they usually request a copy of the RAC review if the protocol was reviewed at a public meeting. The additional effort by company personnel from adding IBC review to the IRB review at each site is generally quite limited, but of course the IBC and clinical trial personnel at each site will expend a variable amount of effort reviewing the documentation. Participation in RAC public meetings involves expenditure of personnel time and the cost of travel for investigators and company personnel.

Annual reports to OBA are prepared as a subset of information submitted to the FDA in IND annual reports. Serious adverse events submitted to FDA on an expedited basis are also submitted to OBA on an expedited basis but have been very uncommon in the gene transfer studies with which I have been involved. In addition to the personnel and travel costs incurred by the company, there are also the personnel costs of the IBC at each participating site and the personnel and travel costs of the RAC members and staff that must also be considered.

Value of RAC Review

It is difficult to quantify the value the RAC review adds to any clinical trial protocol. Each clinical protocol undergoes careful review by the FDA and the IRB for each participating site. For protocols selected for RAC public review, three RAC members provide written comment in advance of the RAC meeting, and additional comments are provided by members and the public at the meeting. The scope of these comments is variable and rarely identifies a critical issue not identified during review by FDA or the IRBs. Many of the RAC comments are incorporated into the final design, analysis plan, or informed consent documents for the protocol, but because the RAC has an advisory and not a regulatory role, the sponsor has leeway in how to respond to these comments and suggestions.

Impact on Financial Investment

During fundraising efforts, potential investors are made aware of the requirement for RAC review of clinical trial protocols and are provided access to previous OBA submissions and RAC public reviews of clinical trial protocols. None of the investors have articulated that RAC review was a factor in their investment decision. However, investors are clearly supportive of any changes that will reduce the overall costs associated with bringing any new product to market.

Overall Conclusions

Based on personal experience with the RAC, compliance with the *NIH Guidelines* is not overly burdensome and adds

relatively little to the cost of developing products that use recombinant DNA technology. The gene transfer vectors used by the companies I have worked for have an excellent safety record, the scientific basis for their use is much more advanced than it was during the early decades after the RAC was established, and it is not clear whether continuing review of every gene transfer clinical protocol remains useful.

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Nicholas Dainiak

This perspective on the scientific necessity for continued additional oversight of gene transfer therapy was presented to an *ad hoc* committee of the Institute of Medicine on August 6, 2013, where I served as a panelist on the Patient Advocacy Efforts and Perspectives session. It presents the views of a clinician, administrator, and physician scientist whose professional background includes nearly 20 years of continuous R01, R13, M01, and other funding from the NIH for research on the regulation of hematopoietic stem cell differentiation/proliferation, and subsequent funding from the DOD for research in radiation biology and radiation effects. These views are mine, reflecting my unusual background, and do not and cannot precisely mirror those of other families whose experience with the horrific effects of Batten Disease (BD) is as unique as their beautiful children with this disease. Nevertheless, I believe that at least some, if not most, of my comments will strike a chord with all of the families.

What Families Do When No One Knows the Answer

My grandson, Nicholas, was admitted to the Children's Hospital of Boston in September 2008, where he was diagnosed with BD at the age of 5½ years. Our family was overjoyed with Nicholas and had every expectation that he would be a happy and healthy child, replete with dreams and aspirations of a young boy. And he was—perfectly healthy—until he turned 4 years old, when he had his first seizure. Medications were started by a neurologist after two additional seizures, and a neurological work-up revealed a normal MRI and EEG. The immediate and extended family worked to raise money for childhood epilepsy. However, seizures continued and Nicholas required eyeglasses, which initially helped only slightly. Two separate ophthalmologic examinations did not detect a problem for what turned out to be rapid visual loss. Nicholas began having visual hallucinations, prompting admission to Children's Hospital in Boston, where the initial diagnosis was thought to be medication toxicity. The diagnosis of BD was first suspected by a third ophthalmologist, who relayed this information to my son, who is a gastroenterologist. This disease was so rare that its name did not trigger the sense of dread that would later become our reality. Fundoscopic examination revealed characteristic retinal deposits, and a skin biopsy showed the inclusion bodies that characterize BD. Nicholas was found to have the CLN2 splice mutation 523-1 G>C, g.3556 G>C with homozygous polymorphism g.3767 T>C, and the diagnosis of late infantile neuronal ceroid lipofuscinosis (LINCL) was confirmed.

Delayed diagnosis is the rule in BD. Pediatricians, pediatric neurologists, and ophthalmologists rarely have prior experience and rarely suspect the diagnosis. Frustrated by lack of an answer that explains childhood seizures, poor vision, mental retardation, or even schizophrenia, families anxiously send their child from one subspecialist to another. When they receive the diagnosis, they Google BD and, like my immediate family of physicians, dentists, and healthcare advisors, are horrified to learn that mortality is 100% in approximately 10 years. They are then presented with an essential contradiction, an absurdity: their child, who has developed normally, will now die.

Families cannot find peers, relatives, friends, or health care professionals with whom to discuss their tragic situation. They search the web, find the Batten Disease Support & Research Association, and receive the empathy they crave. They learn of a few clinical trials having limited accrual and little chance for success. They form foundations such as *Our Promise to Nicholas* to raise money for research so that their children and those of others who will be diagnosed in the future will have hope. They scour the literature for treatments that may have even a remote chance of helping their child. Families try to adapt to their new identity with BD, an identity that originates in their very own DNA. They must act quickly since disease progression (apoptosis resulting from intracellular lipofuscin deposits) is rapid and relentless. They feel lonely, guilty, and hopeless. No one knows about BD. Aside from supportive care (*i.e.*, anti-seizure medications, physical therapy, nutritional supplements, and perhaps a feeding tube), there is no treatment for BD.

What Families Need When New Clinical Trials Are Available

Daily, families follow the web for any evidence of new potential therapy of BD. When largely unregulated stem cell companies in China offered treatment for neurological disorders, some brought their children to China for consideration of stem cell transplantation. Cost is no object when every day you observe further decline in your child's function. Yet controversy erupted over stem cell tourism in China, people traveling to receive unproven treatments with potential lethal consequences, as it was damaging to stem

cell researchers worldwide (1,2). Over 100 laboratories in China were offering stem cell procedures, many of them unregulated at the time (3). Little to no information was available concerning adverse events, safety, and efficacy of stem cell procedures. Evidence-based outcomes were not available, as prospective studies were rarely or never conducted.

When a U.S. company published preclinical findings (4) and announced in a press release (5) that its proprietary, purified human neural stem cells migrated extensively throughout the host brain, reduced the accumulation of lipofuscin, and delayed the loss of motor function in a mouse model of INCL, parents hoped with all their heart that their child would be accepted into a clinical trial of neural stem cells, even though there was only proof-of-concept data to support such a trial. Some parents were willing to consider therapy at the earliest stage of disease, as a new trial was announced at an INCL/LINCL workshop that was held on November 11–12, 2010, in Bethesda, MD. This workshop was supported by the National Institute of Neurological Disorders and Stroke, *Blake's Purpose, Drew's Hope Research Foundation, Fight for Nicholas, Hope 4 Bridget, Jasper Against Batten, Mary Payton's Miracle Foundation, Noah's Hope,* and *Our Promise to Nicholas Foundation*. Conferees included not only scientists but also BD families and representatives of their respective foundations.

Families with newly diagnosed children, ages 6 months to 6 years old, were invited to participate in the new trial. There were no plans to follow an untreated ''control'' group. Consternation and sorrow were deeply felt by parents when it was learned following the Bethesda meeting that the trial would not move forward, even though results presented at the Bethesda meeting (and also presented in February 2010 at a Lysosomal Disease Network symposium in Miami) of a recently completed phase 1 trial in six children with INCL/LINCL included 1 death (thought to be unrelated to therapy) and 16 adverse events, including fever, seizures, respiratory insufficiency, and dysphagia, requiring placement of a gastric tube (6). Moreover, during the discussion of the phase 1 trial presentation at the Bethesda meeting, it was disclosed that no evidence for cell migration, differentiation, or cell division was found at autopsy in the recipient who expired. I argued that even if risks were minimized and neural cell differentiation and proliferation had occurred, such growth required regulation. Nevertheless, family support for the new neural stem cell trial was so strong that complications of the phase 1 trial were stricken from a meeting summary that was prepared for the NIH in hopes that there would be no impact on plans to implement the new trial, the new chance for a cure.

Hopes were high among families when it was learned that neurological assessments would be conducted at Weil-Cornell for accrual to the #0904-977 trial of rh.10 expressing human CLN2 cDNA in LINCL (7). All hoped that their child would meet inclusion criteria for the trial. Unfortunately, the clinical course of BD is highly variable among children and the rate of progression over time for a given child is also highly variable. On initial evaluation in March 2010, my grandson just met the criteria at the high functioning end of the scale for each of the categories. My son and I accessed the June 16–17, 2009, RAC review of the trial (8). I was comforted to know that my primary concerns were discussed, including validity of the in-house performance scale and guidelines for stopping the trial.

Informed consent was provided in the usual fashion. However, my son was dismayed that there was an additional delay of 5 months (to August 2010) attributed to responses to RAC. During these 5 months, significant deterioration of all scores took place. Fortunately, Nicholas was still eligible for the trial, although now at the low functioning end of the scale for each of the categories. We were and are today grateful to have had the opportunity for Nicholas to participate in the trial. An advocate was assigned to the family (who was found to be very helpful and supportive throughout the course of the hospitalization and during the post-procedure period). Repeat informed consent was provided prior to treatment but this time it was perceived by my son (who himself has participated as an investigator in clinical research) that it was made emphatically clear that Nicholas would not benefit from the treatment. My son weighed the new comments as largely due to RAC input, which he considered to be unhelpful. Other children were not as lucky as Nicholas. In one case, a child functioned too well on initial evaluation, only to miss eligibility criteria by functioning too poorly on subsequent neurological evaluation. How heartbreaking!

Families are necessarily in a highly emotional state of mind when considering therapeutic options for BD. Because they are dealing with certain death of their child, families think with their hearts, hoping for a novel therapeutic option that may slow or stop progression of disease. They minimize the importance of research oversight, particularly when an IRB has been involved in the consent process. They do not distinguish between oversight by a local IRB and oversight by a national ethics panel or scientific body. BD families suspect that clinical trials in other countries are ethical, and they assume that oversight of clinical trials in the United States is appropriate. Nevertheless, they generally view oversight as a barrier to the development of new therapies. They are on a continual quest to find a cure for BD, particularly while their child is alive. This quest becomes a significant, if not central, mission of their life. When I recently contacted several of the families whose children underwent gene transfer about the issue of research oversight, they responded with a general lack of awareness that RAC oversight takes place. Oversight is not on their radar screen. Even though they may not be cognizant of it, families need objective assurance that the potential benefits of a new treatment option or untested management strategy outweigh its potential risks. Therefore, I believe that a national body and/or the scientific community should provide additional oversight as a surrogate for families whose objectivity has been lost in their quest to find a cure.

Scientists and clinical investigators are not accustomed to working with families in this state of mind. They usually rely on satisfying requirements of the IRB. However, many (if not most) IRBs are not accustomed to counseling families that have such a burning need to find new therapeutic options. I believe that many (but not all) scientists and IRBs benefit from the enhanced oversight provided by the RAC. Furthermore, in cases such as cell-based therapy for BD, additional scientific oversight is warranted.

Recommendations for Oversight by the RAC

Today, gene therapy remains a potentially promising, active area of research in medicine. It is a particularly

attractive option for the treatment of monogenic disorders such as severe combined immunodeficiency disease, chronic granulomatous disease, clotting factor deficiencies, and neurodegenerative diseases such as BD (9). As the field has had setbacks and limited success, scientific and ethical oversight of its programs remains desirable. Based upon the above considerations, I believe that oversight bodies should be vigilant in assessing the probability and degree of risks and benefits of an intervention to children with BD. The RAC provides a unique service that may be beneficial to not only families but also researchers and IRBs. However, in their work, the RAC should be timely and avoid delays in auditing gene transfer studies for BD, as the ''window'' for objective assessment of decline in neurological function is frequently very narrow. A few months may make the difference for any given child. It is devastating to families whose children ''miss'' cutoffs for eligibility due to delays created by the RAC. Specific recommendations are as follows.

1. RAC deliberations should be timely and concise. Delays in trial approval should be based on elucidation and resolution of critical issues that have been prioritized as highly significant.
2. In the case of INCL/LINCL, it is difficult to study older children, as their disease has often progressed and progression is irreversible. An exception should be made to the general practice of studying older children before studying younger children.
3. Informed consent for gene transfer trials in BD is complicated by the highly driven need of families to ''find a cure.'' While a ''zero'' benefit is inappropriate, families must understand that the primary goal of the trial is to answer a scientific question rather than to cure the enrollee. Consideration should be given to formally assess understanding of the trial during interviews. A short (3–5 questions) assessment may suffice.
4. Due to rapid progression and highly variable rates of progression of different signs and symptoms (i.e., seizure activity, loss of vision, lack of coordination, personality changes, mental deterioration, impaired ventilation), criteria based on degree of function rather than on duration of disease or age of child should be employed.
5. Due to high variability in clinical course among children with INCL/LINCL, care should be taken when assigning a new neurological finding to the vector rather than due to the surgical procedure or to the disease per se.
6. Seasoned investigators who have significant experience with gene transfer require less oversight than do novice gene therapists. The RAC should take into account the experience and prior track record of the principle investigator, as well as the infrastructure available for the study.
7. IRBs with limited to no experience with managing gene transfer studies may require more scientific oversight than IRBs that are experienced in gene therapy trials. The RAC may need to modify the extent and scope of their review, depending on past experience of the local IRB.
8. Since objective methods to assess neurological function, mood, and cognition in mice are difficult to identify, care should be taken when evaluating evidence presented from preclinical murine studies.
9. Stem cell therapy presents its own risks, such as unregulated growth, malignant transformation, and immunological complications. Because gene transfection of stem cell populations is potentially applicable to BD, the RAC should carefully review proposals that involve the use of transfected stem cells from the point of view of regulation of stem cell renewal, differentiation, and growth, as well as from their potential to produce gene product.
10. Conflicts of interest of the investigators should be carefully documented and discussed with participants in the trial. Families should have an understanding of the financial incentives of all relevant investigators in the trial.
11. By all means, the RAC should understand that for some diseases, 100% mortality is the only option left for children when a trial does not proceed. In such instances, the goal of ''not doing harm'' by perfecting a trial has the unintended result of leaving a family without hope and a child without a chance at life.

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I am Jennifer Farmer, executive director for the Friedreich's Ataxia Research Alliance. I am a genetic counselor with almost 20 years of clinical, research, and advocacy experience on neurodegenerative diseases, with Friedreich's ataxia (FA) being my primary focus for the last 10 years.

In my role as executive director, I oversee FARA's research portfolio (funding basic, translational, and clinical research grants, as well as partnership development) and Patient Registry and Collaborative Clinical Research Network (multicenter natural history, clinical outcome measure, and biomarker studies).

The drug development pipeline for FA is quite diverse—small molecules, gene therapy, stem cell therapy. Several drug candidates are presently in clinical trials or have been through trials. We have had experience mostly with small molecules in seeking regulatory approvals for clinical research.

- Participated in pretrial planning meetings with sponsors and investigators for P1, P2, and P3 studies
- Participated in pre-IND meetings
- Sponsored investigator-initiated clinical trials

My clinical experience shortly after the disease gene was identified, >15 years ago, and providing genetic diagnosis patients—patients were asking about gene therapy as a therapeutic option. I bring this up because patients/families are not naïve to concepts of gene or genetic therapies. In fact, many well-educated patients clearly articulate why these therapies are likely to have the most profound therapeutic benefit to them in the long run.

While we have not had gene therapy trials in FA, we do have very compelling animal data with AAV vectors that are moving forward, and there are several academic and for-profit groups working on RNA therapeutics approaches for FA. Ensuring adequate review of preclinical and clinical development and patient safety through the regulatory review process is very important for the FA patient community.

Background

Friedreich ataxia is a rare autosomal recessive condition that is caused by mutations in a single gene. The mutation that accounts for >95% of cases occurs in an intron and results in a silencing of gene transcription. This silencing is not 100% so individuals with FA make about 5–20% of the associated protein frataxin.

The phenotype has considerable variability, however, most individual's present during childhood or early adulthood with gait and balance problems and sensory loss. The disease is progressive and most individuals lose the ability to walk about 8 years after symptom onset. In addition to a progressive neurological phenotype there are other organ systems affected—cardiac, endocrine, musculoskeletal. About 30% of individuals with FA develop a hypertrophic cardiomyopathy that leads to CHF and significant morbidity and mortality by their early 20's or 30's.

In some ways FA is an ideal candidate for genetic therapy approach—genetically homogenous (easy to diagnosis), mutation is in an intron, patients make some of the protein encoded by the target gene (just not enough), and there is a therapeutic window (childhood or later onset with relatively slow progression).

FA is a progressive disease that will result in loss of independence and the ability to perform most ADLs and carries significant risk for premature death from cardiac disease and spares cognitive function. There is no treatment, consequently, there are high unmet medical needs.

While the gene therapy field was in its infancy 20 years ago, that does not seem to be the case today.

While not having had the direct experience of participating in a RAC review of a gene therapy protocol for FA, I do appreciate that such a process certainly can provide benefits both to the scientific validity and integrity and to the protection of human subjects. However, it seems the field has grown and matured and this type of consultation and support now exists on its own now in the greater research community. Evidence of this was provided at the June 6th meeting—RAC is waiving review of the majority of protocols received. In addition, the FDA has published guidance on the design of early phase gene therapy trials.

How is gene therapy different? Why the extra external review?

New technologies do require special attention and evaluation, but where do we draw the line?

There should be equal oversight for all human subjects research and clinical trials.

The FDA and IRBs should be given ongoing training and access to outside experts and advisors to perform adequate review. Otherwise special committees for all sorts of new drugs, devices, interventions, would be continuously created and each would evolve its own special process for seeking review.

The data presented at the June 6th meeting on the number of protocols submitted makes it hard to argue that there is little experience in gene therapy.

One key concern from FA community is time.

The time it takes to get through the regulatory process (both federal and local) is a major issue that patients have expressed great concern and frustration over. Significant time is taken in submitting protocols, waiting for meetings, and waiting for responses. Then the time is often further prolonged by the need to respond to changes and clarification—some of these changes and requests can be very helpful and constructive and improve studies, however, often times different regulatory entities issue conflicting statements and requests. The more reviews that occur the more opportunity for conflicting advice and guidance—this can leave a program in a prolonged state of confusion, trying to sort out which changes are in the best interest of the study and subjects and how to advance the program. When there are additional review committees added to this process, there needs to be consideration of the value added of that review versus the net loss in QOL patient's experience during that time. For example, a six-month timeline to a review meeting is a significant amount of time to patients, there is significant neurologic loss that occurs over six months and this can make the difference in being ambulatory versus non-ambulatory.

Having additional levels of review and approval would need to fill a significant safety or expertise gap and have a mechanism for ongoing submission and rapid timeline-driven response for this to be perceived as valuable to the patient community.

Our Experience

Gene therapy experts that we work with speak very highly of the FDA and their role in providing early scientific feedback and guidance into preclinical toxicology, manufacturing, and clinical development plan.

Nearly all investigators and companies engage the patient community early in their clinical development planning, especially for rare disease.

There are increasing mechanisms and opportunities for patients to be involved and provide a voice at the regulatory meetings (PDUFA V legislation).

The RAC has clearly provided an important role in helping advance gene and cell therapy, especially when there was a lack of expertise in the regulatory community. However the environment has changed as the field has matured and many of the functions of the RAC can be fulfilled by the local and federal regulatory bodies.

Patients with rare disease are experts on their disease. Patients want the ability to be directly involved in making risk–benefit decisions with experimental therapies and these mechanisms are increasingly available both through FDA and local IRBs. Time is critical to patients with progressive disease—each day there is loss that might not be returned even with therapy that can reverse the disease at a cellular level. Experimental drugs, devices, and interventions for untreatable conditions need to have equal, informed, rapid, and transparent oversight to ensure an effective and expeditious path to the clinic.

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Henry T. Greely

What technology had the greatest influence on twentieth-century America? One can certainly name many contenders, from antibiotics to television, from contraception to electrification. Perhaps influenced by the fact that I am a Californian, I would nominate the automobile. It changed the shapes of our cities, pathways of our pair bonding, and ultimately the very air we breathe and climate we live in. It also was an explosive technology. It is estimated that the United States held 300 cars in 1895; 8,000 in 1900; 78,000 in 1905; 460,000 in 1910; and 1.7 million in 1914.

As far as I know, no one did a technology assessment of the automobile in 1900. No government agency sat down to think about the implications of the growing use of the automobile for urban planning, shopping patterns, premarital sex, or climate change. If someone had tried, rigorously or systematically, to predict the future of the car, they would almost certainly have gone wrong. No one was watching close to see how motor vehicle use was developing and what unforeseen issues it was bringing up that needed attention. And even if these hypothetical futurists had been right, no one would have believed them let alone acted on their predictions.

Today we do try, in a more organized way, to predict the future course of new technologies and their implications for our societies, through think tanks, academics, corporate departments, and occasional government commissions or agencies. For complicated reasons, we do this more with interventions that are directly aimed at human health than in other realms. It is by no means clear whether, and to what extent, we have succeeded—or failed.

Your committee has been asked to review and assess the activities of the NIH Recombinant DNA Advisory Committee. You have asked this panel to address the need for oversight of controversial science. I think it will be useful to look at this question both very broadly, in terms of the virtues (and vices) of technology assessment in various incarnations, and very narrowly, drawing on experience with one recent method for oversight of controversial science, the Embryonic Stem Cell Research Oversight (ESCRO) committees. This short and informal article, which I have written on short notice for this panel, is my effort to begin to think about these issues. It starts by generalizing about how ''oversight of controversial science'' might be useful. It then talks about recent oversight of controversial science, seeming to have focused on the biosciences. Third, it tries to draw some lessons from the ongoing ESCRO experience. It concludes with some very tentative thoughts about what worthwhile system for oversight of controversial science might look like.

Oversight of Controversial Science and the Ends It Serves

The word ''oversight'' can mean many things including, ironically, as a noun, a forgetful failure to notice or observe (an ''oversight''). In the context of this panel, when I talk about oversight, I will refer to some process of continued attention to the ways in which a new technology is being applied and how it is developing, with some concern for both the technology's safety and its broader social implications. Thus, a company introducing a new technology—say, Apple with the iPod, the iPhone, or the iPad—will likely pay attention to how the technology is being used, but without substantial concern for the broader social implications, or, apart from some concern about product liability litigation, whether the technology is safe. The oversight method may be tied solely to one technology, like the RAC

or ESCROs, or may be more general, perhaps with a wider mission but one that also picks up new technologies, like IRBs or the FDA's investigational new drug exemptions (INDs) or investigational device exemptions (IDEs). Although there certainly may be more, I see four plausible ends served by oversight of controversial science: assuring safety and ethical standards, observation, guidance, and reassurance.

First, an oversight process can help protect people with whom, on whom, or to whom the new technology is first being applied. It can also watch, and intervene, to make sure that ethical lines are not crossed. The IRB process does this with new technologies (as well as older technologies) as they are being deployed in human subjects research. The mere requirements that researchers provide a protocol, detail their consent processes, and in fact obtain informed consent are some protections for safety. So is the requirement that the IRB balance risks and benefits of the research. In a broader sense the FDA drug and device approval regime also plays a role in assessing the safety of new technologies.

Second, a continuing oversight process provides a way to observe the technology. One can see at least three kinds of problems (or their absence). Some problems will come up in a protocol development phase. The NAS Guidelines on Human Embryonic Stem Cell Research required that nonhuman animals that had received human embryonic stem cells or their derivatives not be bred; what that actually meant had to be figured out as protocols were written, and reviewed, to meet that requirement. Other problems are observed in the course of the technology's development and adoption. The reporting of unanticipated problems to IRBs or the use of data safety monitoring boards are examples of this effect. And finally some observation will help the oversight group see how the technology is being used. The existence of the RAC, for example, made it easier to see the kinds of diseases researchers were trying to use gene transfer to treat and how that changed over time.

The guidance benefits are really the result of the safety and observation benefits. The oversight group can, sometimes, see things that have worked and those that have not and suggest, either to individual investigators or adopters or more generally, some best practices for proceeding.

Finally, and of a different type, an oversight process can provide some reassurance that may be politically (or commercially) important. The very idea that someone is watching and worrying about the new technology can make the technology more acceptable. It seems quite likely to me, though I cannot prove it, that the ELSI program was included in the U.S. portion of the Human Genome Project in large part as a way of weakening political opposition based on the risks of the Project. It seems likely that the ESCRO requirement of the NAS stem cell guidelines came, at least to some extent, from a similar motive.

Why Have the Biosciences Been Special?

Almost all of the examples I can bring to mind of oversight of controversial science have taken place in the biosciences and especially the *human* biosciences. This may be the result of my own background and work—I may just be parochial. But I think this imbalance is real. Four main reasons explain it, one going to when science *is* controversial, but the other three depending on unique or unusual aspects of the biosciences.

New technologies in the biosciences are, I think, more likely to be ''controversial science'' than non-bioscience technologies because *we* are biological organisms. They implicate our selves (or the selves of our biological cousins) and not just our tools. This is often disconcerting. (And, in fact, controversial science about nonhuman bioscience seems more controversial when it more closely affects us—genetically modified organisms that we *eat* have been more controversial than genetically modified organisms that we wear, such as cotton.) Cloning was worrisome, in the early 1970s stories were one of the contributing sources of modern bioethics, mainly because cloned humans made us worry about ourselves. Some non-bioscience technologies may be controversial because they threaten to displace us (robots or artificial intelligence) or because they threaten to extinguish us (some of the fears about some nuclear research), but I think they are all controversial ultimately because their connections to us—and, for us, everything is all about us.

That is one reason, but not the only reason, for the disproportionate attention to the biosciences. Also crucial are the numbers of ''hooks'' that make it legally and politically easier to have oversight in the biosciences. I would point to three in particular: the FDA, human subjects research, and federal research spending.

Apple did not have to get governmental approval before releasing the iPod, except perhaps to the extent of making sure its electronics did not cause dangerous interference. It had to interact more with public regulators about its iPhone and iPad, because both use the publicly regulated Wi-Fi and cell phone systems, but it still did not have to convince anyone that, as a general matter, the iPad was safe and effective. Many bioscience products do, including not just drugs and devices but food additives, color additives, and in some cases food. The FDA provides one hook for much controversial bioscience, both in terms of when the science is ready to be used in human experiments (INDs and IDEs) and when it is ready for widespread public use.

The FDA is also one contributor to the ''human subjects research'' hook. Unless an entity is conducting human subjects research with federal research funds from a federal agency that adheres to the Common Rule, is conducting that research pursuant to permission from a relevant agency, or has given an assurance to such an agency that all of its research will follow the Common Rule, it is not bound to the federal regulations that give rise to IRBs. Most of U.S. industry is therefore not bound by the Common Rule, even when it does human subjects research, but bioscience research usually will be. The industrial players—pharmaceutical, biotech, and medtech companie—often are conducting research under INDs or IDEs from the FDA. And the very sizeable academic component of human subjects research almost always is either using federal funding or has given an assurance (usually to the Department of Health and Human Services) that it will follow the Common Rule.

Finally, the federal government, and in some fields state governments, have disproportionate leverage over bioscience research because they fund so much of it. The NIH alone spends about $30 billion each year on biomedical research. The National Science Foundation, the Defense

Department, and other federal agencies add more. If you take government money, the government has the power to impose almost any conditions, including oversight conditions. Although I do not have data on this point, I suspect the federal government funding of bioscience, defined broadly, vastly exceeds its research funding in any other area except perhaps defense and intelligence, both of which have some overlap with biosciences.

This funding hook has allowed some oversight of some other controversial science. Issues around the possible contamination of other planets or asteroids with Earth life (or of the contamination of Earth with alien life) have been considered controversial science with some oversight as a result of federal funding. Some of the public concerns about high-energy physics creating deadly black holes might be said to have led to (very) little oversight, but perhaps mainly because it was being done in federally owned national laboratories or in a foreign projects with U.S. government support (CERN).

What Do ESCROs Teach Us?

I have served on Stanford's ESCRO, and its predecessor body, for nearly a decade. I have served as chair of the California Advisory Committee on Human Stem Cell Research since 2005, and earlier I took an active role as a member of the California Advisory Committee on Human Cloning, whose recommendations about ''non-reproductive cloning'' dealt with some human embryonic stem cell issues. Earlier this year, I published an article on the past, present, and future of ESCROs. This discussion draws heavily on all those experiences.* The ESCRO experience, which has been grossly understudied, holds at least four lessons for your committee.

First, though, let me review the basics of ESCROs for committee members who may not be familiar with them. The ESCROs (SCROs in California, where their jurisdiction goes beyond ''embryonic'' stem cell research) are the brainchild of the NAS Committee on Guidelines for Human Embryonic Stem Cell Research in its 2005 Guidelines for Human Embryonic Stem Cell Research.† Forty or more ESCRO committees are scattered across the United States. Many of them are entirely voluntary; others have been required by state statutes or state funding agencies. (Interesting, the NIH has not required their use in NIH-funded research.) The International Society for Stem Cell Research has also adopted guidelines that recommend ESCROs; I do not know how common such committees are outside the United States.

ESCROs closely resemble IRBs as well as Institutional Animal Care and Use Committees and Institutional Biosafety Committees. They review protocols of some proposed human embryonic (or, in some cases and places, nonembryonic) stem cell research for compliance with the NAS Guidelines or other state or federal rules or guidance. Covered research must be approved by the ESCRO before it can be started. ESCRO approval is also necessary for revisions or renewals and ESCROs must be notified of some kinds of research for which approval is not required. The NAS Guidelines provide some rules and advice on what kinds of research may and may not be approved and subject to what conditions. For some ESCROs, such as the SCROs of California, state laws, regulations, or guidelines supplement the NAS positions.

The first lesson I draw from the ESCRO experience is that someone had to decide that this was controversial science that needed oversight, or, more fundamentally, that it was controversial science that *might* need oversight. The NAS Committee did not itself spring out of the ground. I do not know who had the idea and when, but someone convinced the academies and private funders that a committee to consider human embryonic stem cell research was a good idea. As your committee well knows, NRC and IOM studies are rarely cheap, fast, or easy; it takes some motivated people and institutions to make them happen. Whoever did the pushing that led to this NAS Committee played the first crucial role in the history of ESCROs.

Second, the Committee process was important. It might not have recommended guidelines and those guidelines might not have included ESCROs. The study of the specific problem, in some detail, had a real impact on what happened. For example, along with others, I testified before that committee on the issue of human/nonhuman chimeras. Although I would not claim any substantial personal impact, the issues were discussed before the Committee, in public, and the Committee's Guidelines dealt with them in some detail. That kind of process for crafting an oversight scheme was important.

Third, the protocol review process for the ESCROs has definitely been useful but that value has been declining or, at least, changing. In the early days of human embryonic stem cell research, both before and after the NAS Guidelines, ESCROs would wrestle with questions of whether protocols were sufficient. Just how much evidence of the provenance of stem cell lines (and how good evidence) was needed to decide whether the lines were acceptable? The NAS Guidelines said that animals that had received human embryonic stem cells should not be bred—what protections against breeding were sufficient? Were cells that were not themselves human embryonic stem cells but were derived from such cells covered by the ESCRO process? What about induced pluripotent stem cells? Or, should ESCROs cover the transfer of non-embryonic but multipotent human brain stem cells into nonhuman animals? This was the observation and guidance portion of the oversight. We saw what was happening, tried to figure out sensible ways to respond to it, and created policies, protocols, and templates to deal with it.

But those kinds of questions, not surprisingly, became less common as time went on. Existing questions were answered and fewer arose to take their place. The conclusions the Stanford SCRO reached became embodied in the routines for the SCRO staff and the stem cell researchers, as well in the protocol templates that the staff created and the researchers used. Review became much more routine, more a matter of making sure the researchers had checked the proper boxes. Occasionally new issues arose—the recent

*Henry T. Greely, *Assessing ESCROs: Yesterday and Tomorrow*, The American Journal of Bioethics, 13:1, 44–52 (2013). I recommend the committee look not just at that article, but also at the eight open-peer commentaries that were published with it in the *American Journal on Bioethics*.

†Committee on Guidelines for Human Embryonic Stem Cell Research, *Guidelines for Human Embryonic Stem Cell Research* (2005, Washington, DC: National Academies Press).

announcement that human embryonic stem cells have been derived after (caffeinated) somatic cell nuclear transfer at the Oregon Health Sciences University, starting with human oocytes whose donors had been compensated for more than out-of-pocket expenses, will probably provoke a new round of concern and thought. But the work of the ESCROs, or, at least, of the Stanford SCRO with which I am familiar, has become bureaucratized. This is not a bad thing, but it changes the functions of the ESCRO and serves as a reminder that needs change over time, and institutions, including oversight institutions, will or should change with them.

Finally, the ESCRO experience convinced me that it would have been useful to have more, and more regular, ways for ESCROs to share experiences and advice. The NAS Committee had called for some sort of national advisory group in its initial Guidelines report. That Committee ended up serving something of that role, as it continued for five years after the Guidelines, putting out amendments to the Guidelines in three new reports. An e-mail list serve among ESCROs and people interested in ESCROs provided some help. A group of people grew up to discuss different questions raised by laws and regulations in different states. And the International Society for Stem Cell Research played some role in communicating experience and recommendations. But, as someone in the trenches of both a SCRO and the California Advisory Committee, more communication—or perhaps more drawing of lessons from different experiences—would have been useful.

Thoughts on a System of Oversight of Controversial Bioscience

What would a good oversight system for controversial science look like? I don't think there is any ''one'' good system. Some things, though, would be important in any system; the importance of others will vary from technology to technology and science to science.

First, any effort at oversight of controversial science will have to spot controversial science. This can happen on an *ad hoc* basis, as Congress, the White House, or private bodies respond to particular issues and decide they need oversight. Examples might include the NIH, prodded by Congress, creating the RAC; James Watson, with an eye to congressional and public reaction, creating the ELSI program; and the NAS Committee, funded by various foundations, in creating its Guidelines.

Ad hoc solutions do have some virtues, but reliance on them may miss, or mistake, many areas of controversial science. It might be better to have some kind of permanent body whose mission was to scan the horizon, identify possibly controversial sciences, and take first steps toward suggesting a response, which might include, for example, an NRC or IOM committee. I know of no such body, in the United States or elsewhere. The now very late, but still lamented, Office of Technology Assessment might have filled such a role. The various presidential bioethics commissions could, in theory, fill this role, but they have come and gone with each administration, focusing on particular issues with their volunteer members rather than spotting issues with full-time professionals. A nongovernmental body, supported by philanthropy, might have advantages of (relative) permanence and political detachment. The Nuffield Council on Bioethics in the United Kingdom might be an example of such a body. Of course, the work of independent scholars and activists might also serve this role, but a distinct body assigned to this task could have some advantages to permanence, professionalism, experience over a range of technologies, and credibility.

If this spotting organization identifies an area of controversial science, what would happen next? Ideally, some group would take it farther, exploring the field to see both whether it truly merited oversight and, if so, what kind of oversight would be appropriate. The NAS Committee of Human Embryonic Stem Cell Research is a very nice example of such a next step. Arguably, the ELSI programs system of grants, both to individual researchers and to centers of excellence, could be another.

In this idealized system, a permanent body looks for controversial science that *might* need oversight. A different body, group, or organization then investigates and makes recommendations on whether oversight is, in fact, appropriate and, if so, what kind of oversight. One would want that body to weigh the potential benefits of oversight—in assuring safety, in observation, in guidance, and in reassurance—against the costs and risks of oversight in making its recommendation.

The harder part may be making a decision on what *kind* or kinds of oversight to recommend. This decision spans several dimensions, including at least:

1) institutional, regional, national, or international bodies;
2) mandatory, ''somewhat mandatory,'' or wholly voluntary participation;
3) open, semi-public, or closed proceedings and results;
4) advisory only or decision-making power;
5) statutorily indefinite life, indeterminate life, term-limited with renewal possible, or strictly term-limited; and
6) universal, selective, or no protocol (or detailed) review.

Just combining the choices sketched above provide 864 different options. I will not go into these options in any detail. With a little thought we can find examples for many of them. As I understand it (which may not be correct), the RAC currently is a national, partially mandatory, open advisory body with indefinite life and selective protocol review. The FDA is a national, mandatory, largely closed decision-making body with a statutorily indeterminate life and universal review within its jurisdiction. ESCROs are institutional bodies that, depending on the state, are mandatory or partially mandatory closed bodies with decision-making powers, indefinite life spans (sometimes statutorily sometimes not), and somewhat selective, somewhat mandatory review. Which combination, or set of combinations, may seem appropriate for a particular case of controversial science will depend enormously on a variety of contexts—the science, the nature of the funding, the relevant regulatory and statutory authority, and so on.

The scanning body finds issues; the investigating body makes recommendations. What happens next depends on whether anyone is convinced to implement the recommendations, using statutes, regulations, funding conditions,

publication conditions, or pure persuasiveness. Construed broadly enough, this proposed ''system'' is the status quo for oversight of controversial science. Someone notices an issue, someone (possibly the same body or possibly someone else) makes recommendations, choosing among a host of possible structures; and those involved either do or do not implement some version of the recommendations.

I think the key difference in my suggestion is the first body, the permanent, professional group that looks for scientific issues that might need oversight. Such a group might or might not have any legal power, but its expertise and growing experience should give its suggestions some power that might lead to action. The body could be created by a private foundation. It could also be a small office created by a government body. The body that created it would, undoubtedly, have some effects on the scope of its work. If, for example, the National Institutes of Health were to set up such an office, its scope would no doubt be restricted to the biosciences. Ideally, one might want a body with a broader basis that could look at issues across science. Although the biosciences may be particularly likely to involve controversial science, information technology, physics, agriculture, earth sciences, climate science, and other fields will also provoke important controversies. Yet as the past shows us, human societies, like evolution, are opportunistic. If the best opportunities for useful interventions are in the biosciences, it would not be surprising if the first strong effort to promote useful oversight of controversial science came in the biosciences.

Conclusions

Would the ''controversial science spotting'' institution I suggest actually do any good? I don't know. We have shockingly little decent information about whether various methods of science oversight have been useful or harmful—or even what differences, exactly, they made. The RAC, IRBs, IACUCs, Biosafety Committees, the ELSI program—it is hard to weigh the largely unsought evidence. I suspect the FDA has, on balance, been useful, but others would disagree. My article on ESCROs concluded that they had probably been beneficial, mainly for their reassurance function, though the article admitted that I could not prove it. Whatever we think about the oversight of controversial science, it would be wonderful to have more evidence about its effects, as well as the effects of its absence.

And yet, for reasons that may be more faith based than evidence based, I will continue to believe that intelligence, hard work, and forethought can affect the future in a positive way. To some extent. From time to time. That's not a ringing endorsement, but it's the best I can do. I hope it is helpful.

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