
RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

December 11, 2014

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health**

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[Note: The latest Human Gene Transfer Protocol List can be found on the Office of Biotechnology Activities website at <http://osp.od.nih.gov/office-biotechnology-activities/biomedical-technology-assessment-recombinant-dna-advisory-committee/human-gene-transfer-protocols-registered-oba>.]

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
Minutes of Meeting¹**

December 11, 2014

The Recombinant DNA Advisory Committee (RAC) convened for its 140th meeting at 8:30 a.m. on December 11, 2014, at the National Institutes of Health (NIH), Building 45, Conference Room E1/E2, Bethesda, Maryland. Dr. Donald B. Kohn (RAC Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:30 a.m. until 4:47 p.m. on December 11, 2014. The following individuals were present, either in person or by teleconference, for all or part of the December 2014 RAC meeting.

Committee Members

Scott Antonia, University of South Florida
Michael Atkins, Georgetown University School of Medicine
Tianxi Cai, Harvard University (*via teleconference*)
Saswati Chatterjee, City of Hope National Medical Center
William Curry, Harvard Medical School
Kevin Donahue, University of Massachusetts Medical School (*via teleconference*)
Rebecca Dresser, Washington University School of Law
Marie-Louise Hammarskjöld, University of Virginia School of Medicine
Angelica Hardison, Georgia Regents University
Patrick Hearing, Stony Brook University
Howard Kaufman, Robert Wood Johnson Medical School/Rutgers, The State University of New Jersey
Hans-Peter Kiem, University of Washington School of Medicine/Fred Hutchinson Cancer Research Center
Donald Kohn (RAC Chair), University of California, Los Angeles
Joseph Pilewski, University of Pittsburgh
Lainie Ross, University of Chicago
Michael Sadelain, Memorial Sloan-Kettering Cancer Center
Dawn Wooley, Wright State University
Laurie Zoloth, Northwestern University

NIH Office of Biotechnology Activities (OBA)

Jacqueline Corrigan-Curay, Office of the Director (OD), National Institutes of Health (NIH)

Nonvoting Agency Representatives

Kristina Borrer, Office for Human Research Protection, NIH
Denise Gavin, U.S. Food and Drug Administration (FDA)

NIH/OD/OBA Staff Members

Morad Hassani
Robert Jambou
Maureen Montgomery
Chris Nice

¹ The Recombinant DNA Advisory Committee is advisory to the NIH, and its recommendations should not be considered as final or accepted. The Office of Biotechnology Activities should be consulted for NIH policy on specific issues.

Gene Rosenthal

Attendees

There were 48 attendees at this 1-day RAC meeting.

Attachments

Attachment I contains a list of RAC members, nonvoting agency and liaison representatives, and attendees present for the bioethics discussions. Attachment II contains a list of public attendees. Attachment III contains a list of abbreviations and acronyms used in this document.

I. Call to Order and Opening Remarks

Dr. Kohn, the RAC Chair, called the meeting to order at 8:30 a.m. on December 11, 2014. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* was published in the *Federal Register* on November 25, 2014 (79 FR 70197). Issues addressed by the RAC at this meeting included a report from the Gene Transfer Safety Assessment Board (GTSAB, a subcommittee of the RAC); an update on one gene transfer protocol previously reviewed by RAC; public review and discussion of one gene transfer protocol; and RAC discussions of ethical issues relevant to gene transfer trials.

RAC members introduced themselves by name, affiliation, and research interests.

Dr. Corrigan-Curay reminded RAC members of the rules of conduct that apply to them as Special Government Employees, read into the record the conflict of interest statement, and suggested that related questions be addressed to the OBA committee management officer.

II. Minutes of RAC Meeting, December 11, 2014

RAC Reviewers: Drs. Chatterjee and Wooley

Dr. Chatterjee noted that she was recused from the review of protocol #1404-1304 but found the rest of the minutes to be accurate. Dr. Wooley found that the minutes were well written and accurately reflected the business that was conducted. No changes to the document were suggested by other RAC members.

A. Committee Motion 1

Dr. Kohn asked the RAC to approve the minutes of the December 11, 2014, RAC meeting. The RAC voted unanimously by voice to do so.

III. Gene Transfer Safety Assessment Board Report

RAC Reviewers: Drs. Antonia, Atkins, Curry, Donahue, Kaufman, Kiem, Kohn, Pilewski, Sadelain, and Whitley

A. GTSAB Report

Dr. Kohn presented the GTSAB report for the fourth quarter of 2014. Within the past 3 months, the OBA received a total of 16 protocol submissions, 15 of which were not selected for public review at this RAC meeting. Of the 15 protocols not selected for public review, 12 were oncology protocols, two were monogenic disease protocols, and one was a heart failure protocol. Among these 15 protocols, three used adeno-associated viruses (AAVs), two used plasmids, two used RNA, two used lentiviruses, two

used adenovirus, one used retroviruses, one used herpes simplex virus, one used measles, and one used attenuated *Listeria monocytogenes*. For the fourth quarter of 2014, the GTSAB reviewed initial and follow-up reports on 17 serious adverse events (SAEs) from 15 protocols. (Information about these trials was made available on the OBA website after this RAC meeting and in the future will be available in the NIH Genetic Modification Clinical Research Information System, also known as GeMCRIS.)

Dr. Kohn provided a snapshot of the distribution of protocols in recent years, by vector and application, after first noting that 1,360 gene transfer protocols were registered with the NIH between 1991 and 2014 and that about 70 to 80 protocols were registered each year in the past 2 years. Between 2010 and 2013, about 25 percent to 33 percent of the trials involved retroviruses or lentiviruses, about 22 percent involved plasmids, and 10 percent to 15 percent involved AAVs or adenoviruses. A similar distribution by vector was seen in 2014. Regarding application, about 79 of the protocols in 2014 were for cancer, compared with 72 percent of the protocols in the prior 8 years. Since 2005, single-gene disorders have accounted for 7 percent to 12 percent of the protocols, while infectious diseases accounted for about 5 percent to 6 percent.

For all of 2014, OBA received notification that 49 new protocols opened. During this quarter, OBA received notification that 11 new protocols opened, four of which were publicly reviewed. Dr. Kohn reported on the following noteworthy changes that represented responses to RAC public review:

- *OBA Protocol #1260, reviewed in December 2013: A Three-Part, Multicenter, Open-Label, Single-Dose Study to Assess the Safety, Tolerability, and Efficacy of Intralabyrinthine (IL) CGF166 in Patients with Severe Hearing Loss.* In response to concerns regarding the biosafety of the investigational product (an adenovirus), disposal of any fluid that leaks from the inner ear during the surgical procedure will be in accord with protocols for biosafety level 2 agents. The informed consent forms have been modified to clearly indicate that this is a gene transfer approach and that once the vector is surgically administered it is not possible to remove the agent.
- *OBA Protocol #1188, reviewed in December 2010: Phase I Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering the Survival Motor Neuron Gene by Self-Complementary AAV9:* The previous definition of dose-limiting toxicity for this study included two Grade 2–related toxicities, but the protocol has been changed to state that an unacceptable toxicity is now defined as the occurrence of any Grade 3 (or higher)–related event. The RAC had expressed concern that the starting dose might not be high enough to provide potential benefit in this first-in-human pediatric study. The starting dose was not changed, however, for two reasons. First, all dose escalation trials must start with the minimally effective dose. Second, the highest planned dose is currently at the maximally achievable dose.
- *OBA Protocol #1219, reviewed in June 2013: A Phase I/II, Open-Label Dose Escalation Study to Evaluate the Safety and Efficacy of Single Doses of TT-034 in Patients with Chronic Hepatitis C (CHC) Infection:* To monitor for changes that would not be expected with chronic hepatitis C infection, tissue obtained by liver biopsy will be evaluated for unusual areas of fibrosis, necrosis, or eosinophilia, as recommended by the RAC.
- *OBA Protocol #1306, reviewed in June 2014: An Open-Label Dose Escalation Study of an Adeno-Associated Virus Vector (scAAV2-P1ND4v2) for Gene Therapy of Leber’s Hereditary Optic Neuropathy (LHON) Caused by the G11778A Mutation in Mitochondrial DNA:* In animal models of this disease, vision was rescued only when the vector with the mutated capsid was used. Future studies will attempt to better understand why mutations in three tyrosine residues (to phenylalanine) in the capsid led to these results. Development of an assay to detect the wild-type protein will be pursued in the future.

Dr. Kohn provided an update to another protocol, OBA protocol #864, “*Gene Transfer for Hemophilia*” (ClinicalTrials.gov number NCT00979238). Results from this study were published in the paper entitled “Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B” (Nathwani et al., 2014). In this study, the patients with severe hemophilia received a single intravenous (IV) infusion of a serotype 8 pseudotyped, self-complementary AAV vector expressing codon-optimized factor IX (scAAV2/8-LP1-hFIXco). A dose-dependent increase in factor IX (1 percent to 6 percent of normal value) was seen over a median period of 3.2 years. In the six subjects in the high-dose group (2×10^{12} vg/kg), the consistent

increase in factor IX resulted in more than 90 percent reduction in both bleeding episodes and use of factor IX concentrate. A transient increase in the mean alanine aminotransferase levels to 86 IU/L (range, 36 to 202 IU/L) occurred during weeks 7 and 10 in four of six patients in the high-dose group, resolving over a median of 5 days (range, 2 to 35 days) after prednisolone therapy. In a follow-up period of up to 3 years, no late toxic effects from the therapy were reported.

B. RAC Discussion

Dr. Atkins asked whether the consent form for OBA protocol #864 indicated whether the intervention could be effective. Dr. Corrigan-Curay commented that protocol #864 was a second trial that used a similar approach but a different vector than the prior trial. Dr. Kohn added that the first study, the Penn-Stanford trial, had several different features from protocol #864, including a different AAV. In response to a question about availability of slides shown during the meeting, Dr. Corrigan-Curay noted that the slides are posted after the meeting and are also available upon request prior to posting.

C. Public Comment

No public comments were offered.

IV. Update on X-SCID Protocol #0810-950: Gene Therapy for SCID-X1 Using a Self-Inactivating (SIN) Gammaretroviral Vector

Presenter: David Williams, M.D., Harvard Medical School, Boston, MA (*via teleconference*)

A. Presentation by Dr. Williams

Dr. Williams provided a brief background of X-linked severe combined immunodeficiency disease (SCID-X1) and summarized results of gene therapy trials investigating potential treatments for the disease, including recently published results from OBA protocol #0810-950, *Gene Therapy for SCID-X1 Using a Self-Inactivating (SIN) Gammaretroviral Vector* (Hacein-Bay-Abina et al., 2014).

SCID-X1 is caused by mutations in the gene encoding the human interleukin 2 (IL-2) gamma chain receptor (IL2RG) located on the X chromosome. This results in a deficiency of T-cells and natural killer (NK) cells as well as B-cell dysfunction. Death from community-acquired or opportunistic infections usually occurs before age 1 unless allogeneic hematopoietic stem cell transplantation (HSCT) is performed. Standard allogeneic HSCT with matched sibling donors is associated with an 85 percent to 90 percent overall survival rate. In other cases, however, the survival rate is lower and the rate of complications, including graft-versus-host disease (GVHD), is higher. Mortality among patients who undergo allogeneic HSCT with ongoing infection, for example, is approximately 50 percent. Several factors make SCID-X1 a good candidate for treatment with gene therapy: The condition is fatal; one of the molecular causes is known; and, because the condition is a hematopoietic stem cell disease, the target cells are accessible for correction.

Previous gene therapy trials conducted in London and Paris (i.e., "SCID1" trials) used a first-generation retroviral vector, called MFG, which expressed the IL-2 receptor gamma chain complementary DNA (cDNA) from a Moloney leukemia virus-based gamma-retrovirus vector. In these studies, 20 infants with SCID-X1 who did not have partially matched parent or sibling donors received an infusion of autologous CD34 cells transduced in the laboratory with cytokine prestimulation. Because of the extent of immunologic deficiency with SCID, no bone marrow preparative regimens were necessary, and transduced cells were infused without any ablative conditioning. This first-generation intervention successfully restored immunity in most patients but resulted in vector-enhanced insertional mutagenesis leading to T-cell acute lymphoblastic leukemia in 25 percent of subjects within 36 months post-infusion (with a latency period of 2 to 5.5 years). Transactivation of the *LMO2* or *CCND2* proto-oncogenes was seen in all five leukemias.

To address the safety issues associated with the use of the MFG vector, the research has proceeded in part with the clinical investigation of a modified second generation self-inactivating (SIN) gamma-retrovirus vector (SCID2) containing a deletion in the U3 viral terminal repeat sequence. The second generation vector has also been modified to express the IL2RG chain from an internal cellular promoter obtained from the elongation factor 1 alpha gene. This study is being conducted under OBA protocol #0810-950 (aka the "SCID2" trial). The study has currently enrolled nine boys with SCID-X1 in on-going parallel trials in Europe and the United States. All subjects received autologous CD34 cells transduced with the SIN gamma-chain retrovirus without preparative conditioning. After approximately 12 to 38 months of follow-up, eight of the nine children are still alive. One child died from an overwhelming adenoviral infection before reconstitution with genetically modified T cells. Of the eight surviving subjects, seven had recovery of peripheral blood T cells that were fully functional and led to resolution of any ongoing infections. The subjects have remained healthy since. The kinetics of CD3+ T-cell recovery were not significantly different from those observed in previous SCID1 trials conducted in Paris and London. By comparison with the first generation MFG vector, the investigators concluded that the modified SCID2 vector retains sufficient efficacy for the treatment of SCID-X1. The long-term effect of the SIN gamma-chain retrovirus on leukemogenesis is not yet known. However, analysis of insertion site locations in the T-cells of subjects treated on protocol #0810-950 revealed significantly less clustering of insertion sites within lymphoid proto-oncogenic regions (e.g., *LMO2*, *MECOM/EVI1* and *CCND2*) than in subjects that were enrolled in the prior SCID1 trial. In addition, no clonal outgrowth has been observed to date in any of the surviving subjects, who have been followed for a median of 33 months (range, 16 to 43 months).

A multi-institutional Phase I/II trial evaluating the treatment of SCID-X1 patients with retrovirus-mediated gene transfer is currently open, with study sites planned in Paris, London, Boston, Cincinnati, and Los Angeles. The scientific questions being explored in this trial include whether a change in vector design improves safety, whether a "weaker" internal promoter can maintain efficacy, and whether deletion of the U3 region leads to any differences in the frequency of integration events and location of integration sites *in vivo*. To date, 12 subjects have enrolled in the study. Preliminary results indicate good transduction, cell yields, and engraftment data for the majority of patients. Thus far, no SAEs related to the investigational agent have been reported. Another trial with the same group of patients is planned ("SCID3") and may involve a change to a lentivirus backbone with the same internal promoter. Preclinical data are being developed in anticipation of this study.

Dr. Williams highlighted and compared the key findings from the SCID1 and SCID2 trials to date. He noted that development of the enhancer-deleted IL2RG vector with "improved safety" characteristics in preclinical models resulted from unique international collaborations with shared costs, basic research work, and progression to clinical trials. In the SCID2 trial, the modified vector has shown evidence of efficacy through T-cell repertoire recovery. A higher vector copy number (VCN) correlated with successful T-cell engraftment. Subjects with a VCN in the CD34+ graft of at least 0.7 copies/cell achieved adequate T-cell reconstitution, which was preceded by an early rise in CD56+ NK cells. The presence of the SIN deletion also correlated with reduced integration near major lymphoid proto-oncogenes. Integration sites on chromosomes differed between the trials, with the presence of the intact enhancer correlating with integration clumps at *EVI1*, *CCND2*, *LMO2*, and other genes of concern. In addition, because the use of SIN-deleted gamma-chain retrovirus vector was not associated with major alterations in global integration site distributions compared to the intact LTR-vector, these results are consistent with "vector driven" cell growth or survival in the SCID1 trials where a number of clones were driven to expand following integration with subsequent alterations leading to clonal outgrowth and transformation of the outgrowth to produce a leukemic event. In a murine preclinical study, although there were more integrations near *EVI1* in mice transplanted with cells transduced with the intact LTR-vector (i.e., in the SCID1 trials), no statistically significant differences were seen between SCID1 and SCID2 integration site data. The preclinical murine model therefore did not predict the difference in performance of the two vectors in the human trials.

B. RAC Discussion

Dr. Kiem asked whether any future trials with a lentiviral vector will initially proceed without conditioning. He also inquired about any impact on direct comparability to the SCID2 trial in terms of B-cell engraftment if use of conditioning differs between studies. Dr. Williams noted that the plan for a trial with the lentiviral vector has not been finalized yet but agreed that use of conditioning will complicate some aspects of comparisons between trials. Based on early data from the multisite study and results from the SCID2 trial, the trial with the lentiviral vector may include low-dose conditioning so that patients are uninfected at the time of infusion. One arm of the study will not include any ablation or conditioning, allowing for direct comparison with infected children enrolled in a previous trial. Using the same internal promoter across studies should allow for consistency in expression of the transgene. The team is planning to request a pre-investigational new drug meeting with FDA for further discussions of these issues in designing the next study.

Dr. Sadelain commented that promoter strength bears on both efficacy and safety and asked whether expression of the IL-2 receptor gamma chain was lower with the vector used in the SCID2 trial compared with the SCID1 trials and, if so, whether this difference might be related to use of different promoters. He noted further the potential downstream impact of reduced expression, such as slower T- and B-cell reconstitution and possibly lessened NK-cell function. In addition, although comparable T-cell numbers were reported for both trials at 3 and 6 months, clonality and T-cell numbers might differ at later time points, with T-cell numbers increasing, for example, through homeostatic proliferation. Dr. Williams explained that analysis of the data from the different trials shows no statistical difference in engraftment and reconstitution of T cells using the previous vector versus the current (modified) vector. Further, because the T-cell repertoire is quite diverse, it is difficult to argue that what is happening is simply engraftment and proliferation of a small number of clones. Dr. Williams added that with the SCID1 trials, which had very rapid engraftment of T cells and a relatively large proportion of subjects who developed leukemia, there was concern that the enhancer was so strong that it was leading to abnormal proliferation. The slower kinetics in the SCID2 trial, in conjunction with the resolution of infections and no cases of leukemia thus far, indicate that the secondary surrogate safety endpoints in this second trial may be predictive of less leukemia in this population. These issues are among the scientific questions being explored in the human trial setting.

Dr. Sadelain also asked whether the investigators expect there to be a difference in the safety profile between the SIN gamma-retrovirus vector and a SIN lentiviral vector. Dr. Williams explained that the proposed change in the backbone is for practical purposes. Use of the SIN gamma-retrovirus requires prestimulation of cells and longer *ex vivo* maintenance of transduced cells than when a lentiviral vector is used. In addition, the other trials all use a lentiviral backbone, and the standard cell manufacturing processing is now completely lentiviral based. While there are theoretical reasons and some limited experimental data suggesting that the integration pattern for a lentiviral backbone might be safer than that for the gamma-retrovirus vector, there are no clear data to demonstrate greater safety with the lentivirus. Dr. Williams noted data from a patient in the thalassemia trial in Paris, which used a lentiviral vector, who had insertional events that did not cause disease but that were associated with the expansion of at least one clone. Whether there are any safety differences between the vectors has not been clearly demonstrated. Thus, for the SCID trials going forward, the change in backbone is driven not by concerns about the safety of the SIN gamma-retrovirus vector but by the application of current good manufacturing practices (cGMP) to the cell manufacturing processes. Dr. Williams and his colleagues have applied for orphan disease drug designation for the current vector with the FDA. The team has been approached by several companies that are interested in possible further development of the product in the future.

Dr. Atkins asked whether the consent document for the SCID trial mentions potential efficacy of this first-in-human use of the modified vector. Dr. Williams replied that, following rigorous review of the protocol and consent by the RAC and the study sites, the investigators were very careful to not mention or imply any possible efficacy of the investigational product. Rather, the consent document explains that one of goals of the trial is to assess whether the product might be effective. In addition, the document informs participants about the leukemias that occurred in the previous trials and discusses the alternative therapy available to them (i.e., a "standard" hematopoietic stem cell transplant). The trial also requires a post-consent independent evaluation by another faculty member at the study site and has the family meet

(after signing the consent form) with the consent monitor to review the consent process and their understanding of the consent, including other available options.

Dr. Atkins also asked whether the consent discusses issues regarding reproductive risks associated with the investigational product and any provisions for pregnancy prevention. Dr. Williams replied that because the intervention is an *ex vivo* gene therapy of only somatic cells, there is essentially no risk of germline transmission of the gene. Any pregnancy that does occur, however, would be discussed and followed. Dr. Kohn asked whether the consent discusses risk of passing on the disease should the participants' lives be extended because of the therapy. Dr. Williams was not certain if the consent mentions this possibility.

Dr. Kohn noted the lack of differences in the integration sites in the mouse-based toxicity studies. Given this lack of effect, what assays or other screening studies should be considered to demonstrate safety in the preclinical phase of this research? Dr. Williams commented that the plasmid-based reporter approach will allow for comparison of the effects of expression of the inserted vector in *LMO2*, which is the most important gene in SCID. Thus, the goal is to determine that the vector does not affect engraftment, which can be tested using either a syngeneic transplant short-term assay or a xenograft assay if CD34 cells are used. The *in vitro* immortalization assay is valuable for myeloid transforming events but has not been validated with any correlation to an *in vivo* phenotype of X-SCID.

Dr. Hammarskjöld inquired about the post-transduction timeframe of the integration analysis. Dr. Williams noted that the analysis was done at 3 months, 6 months, and 1 year. The analysis will be done at additional future time points with ongoing collection of samples. The SCID2 trial also included an integration analysis immediately post-transduction to identify the original integration sites. The SCID1 trials did not include this initial analysis; however, no data suggest that the primary integration pattern between the two vectors would be different.

V. Review and Discussion of Human Gene Transfer Protocol #1410-1352: Pilot Study of Autologous T Cells Redirected to Mesothelin and CD19 with a Chimeric Antigen Receptor in Patients with Metastatic Pancreatic Cancer

Principal Investigator (PI): Andrew Ko, M.D., University of California, San Francisco, CA

Sponsor: Gabriela Plesa M.D., Ph.D., University of Pennsylvania, PA

RAC Reviewers: Professor Dresser, Dr. Kiem, Dr. Kohn

A. Protocol Summary

Pancreatic ductal adenocarcinoma (PDA) is a common, lethal, and treatment-resistant disease for which new therapies are desperately needed. Although PDA accounts for an estimated 2 percent of newly diagnosed malignancies in the United States as of 2006, its 5-year survival rate of less than 5 percent makes it the fourth most common cause of cancer-related death in men and women. While diagnosis at an early stage maximizes the likelihood of long-term survival, only 15 percent to 20 percent of patients present with surgically resectable disease. As a result, the diagnosis of PDA generally occurs late. For patients with metastatic disease, the overall survival is approximately 3 to 6 months with current standard therapies and has not improved over the past several decades, so pancreatic cancer remains a major unresolved health problem and a therapeutic challenge.

Immunotherapy involving modified T cells that express a tumor-specific receptor is a promising approach for the treatment of pancreatic cancer. The proposed research will use lentiviral vectors to introduce two chimeric antigen receptors (CARs) into two separate T-cell products, one against the tumor-associated protein (mesothelin) and one against the CD19 B lineage surface protein. The trial is a single-arm, open-label Phase I pilot study to evaluate the safety and feasibility of combination therapy with T cells expressing a CAR-targeting mesothelin (CART-meso) together with T cells expressing an anti-CD19 CAR (CART19). These modified T cells will be administered to up to 12 patients with metastatic pancreatic

cancer following administration of cyclophosphamide (CTX) to deplete lymphocytes. The CART-meso cells are expected to target the pancreatic cancer cells that are known to express the mesothelin tumor antigen at higher levels than normal tissues. The CART19 therapy is proposed to target the B-cell lineage and impede the anti-CART-meso humoral response; this response is expected due to the murine components of the CART-meso, a single-chain antibody fragment (scFv) that targets mesothelin called SS1.

A humoral response to mesothelin-specific scFv-derived investigational drugs has been documented in other studies. Clinical experience using CART-meso cells in mesothelin-expressing cancers suggests that this intervention may have a safe profile. For the past 4 years, researchers at the University of Pennsylvania have studied the safety of CART-meso cells transiently expressed on autologous T cells in patients with pancreatic cancer or malignant pleural mesothelioma. To date, a total of 11 patients have been infused with CART-meso cells for a total of 75 infusions. Two of the patients evaluated for anti-tumor efficacy showed promising results with CART-meso. One SAE has been reported with the third infusion in the third mesothelioma patient, who had an anaphylactic reaction due to human anti-mouse antibodies (HAMA) isotype switching to IgE; this response is thought to have resulted from the long rest period between the second and third infusions. Eliminating a prolonged interval between CART-cell administrations has prevented this problem. The proposed study plans to co-introduce CART19 to ablate B cells and abrogate an anti-CAR response to prolong activity of the antimesothelin T cells. Several prior recipients of CART19 have developed severe cytokine release syndrome, mostly within the context of subjects with large burdens of CD19+ malignant cells, which may trigger high level CART-cell expansion and activation; the risks of this occurring in subjects not bearing B lineage malignancies is unknown.

In the proposed study, the first six subjects (cohort 1) will receive a single dose of $1-3 \times 10^7$ CART-meso/ m^2 lentiviral transduced CART-meso cells and a single dose of $1-3 \times 10^7$ lentiviral transduced CART19 cells on day 0 following a flat dose of 1.5 grams/ m^2 of cyclophosphamide administered 3 days prior to CART cells (day -3 ± 1). If these doses are safe (i.e., zero or one dose-limiting toxicity [DLT] in six subjects), a second cohort of subjects ($N = 6$) will be treated with $1-3 \times 10^8$ CART-meso/ m^2 and $1-3 \times 10^8$ CART19/ m^2 , again following one flat dose of CTX. On the other hand, if two DLTs occur in cohort 1, the target CART cells dose will be de-escalated 10-fold. All doses will be administered intravenously. Initial safety and research assessments will be done on days 1, 3, 7, 10, 14, and 21 post-infusion. Infusions will be staggered to allow at least 21 days between the first three subjects for safety assessments. After the initial assessment period, participants will be followed every 3 months for 2 years.

B. Written Reviews by RAC Members

Eight RAC members voted for in-depth review and public discussion of this protocol. The trial was found to warrant public review because it involves the administration of two different CART cells and because it is the first trial that proposes using a CART-cell product to suppress a humoral response.

Three RAC members provided written reviews of this proposed Phase I trial.

The reviewers found the study to be well designed and the proposed intervention to be appropriate for the target patient population.

Dr. Kiem asked that clarification regarding the rationale for the starting dose of $1-3 \times 10^8/m^2$ be provided and for the plan to use both cyclophosphamide and CART19 instead of first starting with cyclophosphamide and CART-meso only. Data showing any additive or synergistic effect of these two interventions should be provided. Cyclophosphamide and CART19 each act as immunosuppressives and are likely to affect persistence of the CART-meso cells, so they also have potential off-target effects. In addition, the cells will be stably transduced with a lentiviral vector, which is expected to increase their persistence in comparison with transient expression of the CART construct in the prior study.

Dr. Kiem also asked about any preclinical models or settings in which CART19 and CART-meso have been given together and whether there could be any interaction between the two products.

Dr. Kohn noted that the IgE antibody response in one patient occurred within the context of transient mRNA CAR transduction and repeat dosing. In contrast, the proposed study entails a single dose of lentiviral transduced T cells. It is not known, however, whether antibody responses to the murine components of the CAR would be problematic in limiting T-cell persistence and blunting anti-tumor activity. Similar to Dr. Kiem's query, Dr. Kohn asked whether it would be more informative to treat a first cohort only with the novel anti-mesothelin CART cells (i.e., with the lentivirus vector instead of mRNA) and determine their safety, persistence, and induction of humoral response compared with a second group given both the anti-mesothelin CART cells plus the anti-CD19 CART cells.

Dr. Kohn also asked why the investigators are planning to use the experimental anti-CD19 CART cells (and a new derivative with a humanized extracellular domain) along with the experimental anti-mesothelin CART cells instead of using a more conventional approach to temporarily ablate B cells (e.g., rituximab). A more compelling rationale for this choice should be provided, including whether there is any hypothetical therapeutic advantage to ablating B cells with anti-CD19 CART cells rather than with a monoclonal antibody that would outweigh the potentially greater risks.

Dr. Kohn pointed out that the consent form notes the risks of long-term B-cell aplasia as a result of the anti-CD19 CAR but does not clearly state the burden imposed by long-term IVIG therapy, which entails a monthly IV infusion or a subcutaneous infusion two to three times a week. In addition, the consent form should specify that insertional oncogenesis has occurred in Wiskott-Aldrich and chronic granulomatous disorder trials.

Professor Dresser asked whether there was sufficient justification to expose subjects to the proposed intervention, given the three recent deaths in another protocol using this CD19 CAR. She also inquired about the provisions in place to minimize risks to avoid the lethal effects seen in the other trial.

The reviewers found the informed consent document (ICD) to be well written overall and comprehensive as to what participation in the study entails and the potential risks of participation. All of the reviewers suggested revising the section of the ICD "You may not get any benefit from being in this research study," which they did not find informative. This section should more clearly indicate that it is not known whether the study interventions will provide any benefit, rather than saying that subjects "may not get any benefit" from participating. Professor Dresser suggested using or adapting the language currently in Appendix M-II-A-1-c: "The investigational therapy is not expected to prevent all manifestations of the disease, to halt progress of the disease, or to reverse disease manifestations in seriously ill patients. At best, the investigational agent may halt progression of disease."

In addition, the reviewers pointed out that the statement in the ICD that "you can decide to stop at any time" needs to be revised to ensure that participants understand they cannot stop or withdraw from the intervention after receiving the CART cells, because the gene transduction with lentiviral vector is permanent and the T cells may persist long-term. Thus, "withdrawal" describes withdrawal from monitoring, but the modified cells (i.e., the "drug") may persist and cannot be stopped, once given.

Professor Dresser had the following additional comments and suggested modifications regarding the ICD:

- The information for the planned vs. lower-dose is confusing as currently presented. Clearer explanations are needed for why the planned study dose could not be used and why receiving the lower dose would remove subjects from the study while obligating them to undergo the same procedures and make the same number of visits as participants who remain in the trial.
- Many people will not understand the term apheresis. At first mention of the term, the ICD should either note that it is defined in the list of terms used in the consent form or use a more understandable term in its place.
- Use of the term "treatment" could be misleading to patients. The investigators should use phrasing such as "modified cells and other study procedures" or other words that allude to the intervention's investigational status.

- The investigators should consider providing more detail about the deaths in other studies. The detail provided in the paragraph on cognitive impairment is good example of the level of detail that would be informative to prospective subjects regarding study deaths.
- The implications for subjects if the antibodies interfere with use of these tests are not clear and should be better explained in terms of impact on patients' health care.
- A typo in the section on costs needs to be fixed to read "you or your insurance," instead of "your or your insurance".

C. RAC Discussion

During the meeting, the following additional questions, concerns, or issues were raised by RAC members:

- The reviewers found the presentation to be clear and their concerns and questions to be well addressed.
- Professor Dresser commented that the phrasing in the consent form that study physicians "may recommend" giving a participant the lower T-cell dose might be misinterpreted as meaning that the investigators consider the intervention to be a treatment that is safe. She suggested using language such as "may make available" or "may offer" for clarity and greater accuracy.
- The addition of a glossary of medical and technical terms to the consent document will be helpful. The term apheresis still needs to be defined or linked to the glossary at first mention.
- Although institutions may prefer to use standardized language in some sections of the consent document, including language describing anticipated benefit, it is important to not overstate or imply the probability of individual benefit. The investigators may wish to reconsider using language from Appendix M (per Prof. Dresser's comments) that the investigational therapy is not expected to prevent all manifestations of the disease, halt progress of the disease, or reverse disease manifestations in seriously ill patients. Dr. Kiem suggested looking into benefit language previously provided by the RAC that has been incorporated into other Phase I studies.
- Dr. Kohn found the responses that supported proceeding with the plan to use two different CART cells with lymphodepletion and the proposed dose changes to be generally reasonable, given the design and preliminary results from the University of Pennsylvania (UPenn) study. However, he revisited the question regarding use of CD19 instead of an agent such as rituximab for immune suppression and the impact of the chosen agents on cell persistence and off-target effects. The consent form now includes information about long-term gamma globulin treatment for B-cell aplasia that may result from the anti-CD19 CAR.
- Although there is no evidence of insertional transformation in T cells, the investigators may still want to consider including information about insertional oncogenesis in other diseases.
- Dr. Hammarskjöld asked whether both the humoral and cell-based responses with CART-meso have been monitored in previous studies and whether these responses will be tracked in the proposed trial.
- Dr. Pilewski noted the multiple trials targeting pancreatic cancer and asked how the investigators inform patients about the different protocols and how they prioritize the various studies for patient selection.

D. Investigator Response

1. Written Responses to RAC Reviews

The PI explained that lymphodepletion is known to enhance in vivo engraftment of CART cells in both animal models and humans. As proposed for this study, lymphodepletion with CTX has been used in clinical settings prior to CART cell administration. The rationale for including this step in the proposed protocol is to enhance engraftment of both CART19 and CART-meso. The team's experience at the UPenn treating patients with mesothelin-expressing tumors (mesothelioma and ovarian and pancreatic cancers) with CART-meso cells (identical to those proposed in this protocol) in the absence of lymphodepletion indicates that CART-meso cells engraft at low levels. Results indicate that CART-meso cells expand in peripheral blood for 10 to 20 days after infusion but then become undetectable by day 28 post-infusion. The peak of the expansion phase is approximately 2 logs lower than that observed for the

CART19 cells administered to patients with B-cell malignancies. CD19 CARs have been routinely given with lymphodepleting chemotherapy such as CTX and CTX plus fludarabine, and the effects have been enhanced in humans and in mice. Therefore, the investigators think that lymphodepletion before combination CART administration may improve the engraftment and would allow testing per the study hypotheses.

The rationale for co-administration of CART19 with CART-meso is based on the hypothesis that CART19 induces humoral tolerance to the immunogenic CART-meso cells and consequently may increase the CART-meso window of persistence and efficacy. Data from published literature indicate that B-cell depletion by treatment with anti-CD20 antibody (rituximab) is not effective in inducing humoral tolerance in a non-human primate model of transplantation and in humans. Specifically, while both of these studies indicate that treatment with anti-CD20 monoclonal antibodies (mAb) results in B-cell depletion, serum reduction of the specific antibodies tested is minimal and transient. This could be due to the inefficient depletion of various B-cell types or inefficient antibody access to various tissues. In addition, experience to date in treating B-cell chronic lymphocytic leukemia patients with rituximab indicates that B-cell depletion is not complete and that residual CD19+CD20^{low} cells with suppressive phenotype are not eliminated. Therefore, for the proposed study, the investigators wish to test the hypothesis that CART19 cells will be more effective in depleting B cells (including regulatory B cells) and able to better traffic and target B cells in tissues due to being “living drugs” (compared with the inert antibodies). The investigators have concluded that it is most appropriate to test this hypothesis in patients with metastatic pancreatic cancer.

Regarding questions about the doses to be administered, the study has been revised to include a dose escalation design and a lower starting dose of CART cells. Per the initial design, subjects were to receive a single dose of $1-3 \times 10^8/m^2$ lentiviral transduced CART-meso cells and a single dose of $1-3 \times 10^8/m^2$ lentiviral transduced CART19 cells on day 0 following a flat dose of 1.5 grams/m² of cyclophosphamide administered 3 days prior to CART cells (day -3 ± 1). A 10-fold de-escalation in the dose was planned if two dose-limiting toxicities (DLT) occurred. The newly proposed design is intended to start the study with a dose of $1-3 \times 10^7$ CART-meso/m² and $1-3 \times 10^7$ CART19/m² following one flat dose of CTX (cohort 1); this dose is 10-fold lower than the one proposed in the initial protocol submission. If these doses are safe (i.e., no more than one DLT in six subjects), a second cohort of subjects ($N = 6$) will be treated with $1-3 \times 10^8$ CART-meso/m² and $1-3 \times 10^8$ CART19/m², again following one flat dose of CTX. On the other hand, if two or more DLTs occur in cohort 1, the target CART cells dose will be de-escalated 10-fold.

One of the rationales for reducing the starting doses is that there are safety concerns from newly generated data from an ongoing study at UPenn testing the safety and feasibility of administration of lentiviral transduced CART-meso cells in patients with mesothelin-expressing cancers (protocol #NCT02159716). To date, five subjects have received a dose of $1-3 \times 10^7$ CART-meso/m² in the absence of lymphodepletion. The infusions were well tolerated with no overt toxicities, with the exception of one DLT in one pancreatic cancer patient who had a rapid tumor progression at day 28 post-infusion; this event was associated with biliary tract and portal vein obstruction, septicemia with *Klebsiella* pneumonia followed by infection with *Candida albicans*, and extensive tumor necrosis in the liver. The constellation of clinical findings raised the concern for macrophage activation syndrome versus T cell-induced inflammation, and the subject was treated with steroids to eradicate CART-meso cells; however, a subsequent correlative analysis indicated that CART-meso cells were only detectable in peripheral blood up to day 21 post-infusion, whereas the patient survived for more than 60 days following CART-meso infusion.

The PI noted that insertional oncogenesis has not been reported with T-cell therapies. The written response to the reviewers' comments describes the team's experience in the past 15 years with gene-modified T cells and shows that there has not been a single SAE in more than 1000 patient-years of exposure. The PI commented that this safety record is much better than the known risks of oncogenesis following cytotoxic chemotherapy, which occur in 1 to 5 percent of long-term survivors of acute myeloid leukemia who have received chemotherapy. The outcome would likely be the same in long-term survivors of pancreatic cancer.

The team has now infused more than 125 patients with CART19, resulting in a lower rate of SAEs than would be expected from administration of standard-of-care chemotherapy. Cancer patients have been given CD20-depleting mAb to deplete B cells. The investigators are not aware of any cases where patients have been given anti-mesothelin and anti-B cell mAb together. Data indicate that immune suppression enhances the antitumor efficacy of anti-mesothelin antibodies, and there is no reason to suggest that there will be increased toxicity from the combined administration of CART19 and CART-meso. The investigators expect the addition of CART19 to CART-meso to have acceptable toxicity in patients with metastatic pancreatic cancer. The stopping rules in the protocol will be clearly defined to include any toxicity with the combination.

The team's experience at UPenn treating patients with B-cell malignancies with CART19 cells includes the death of 3 out of 125 subjects, for an overall death rate of 2.4 percent. (In contrast, metastatic pancreatic cancer has a 100 percent death rate.) Some of these events were related to the study treatment and occurred in the context of cytokine release syndrome (CRS) and septicemia, while others were caused by disease progression and related complications. The written response to the reviewers' comments includes a summary of these events through October 2014. Two deaths occurred due to CRS associated with septicemia (*Stenotrophomonas* and *Pseudomonas*) following persistent neutropenia; the third death was due to sepsis with influenza pneumonia. The protocol was revised to decrease the CART19 dose to $1-3 \times 10^7/m^2$ and to address the neutropenia as a risk factor for infections. The risk for CART19-induced CRS in non-B cell malignancies, such as solid tumors, is not known. The risk of CRS is strongly related to the degree of tumor burden (and not normal B cells) in patients with B-cell malignancies. Data in the literature suggest that B-cell depletion using rituximab in autoimmune settings or in cancer patients is not associated with CRS.

The investigators have made several changes to the study design in an effort to minimize risks to subjects. These provisions include a 10-fold lower starting dose than previously planned for both CART cells products for the first cohort of patients (cohort 1), more stringent criteria for determining whether the initial regimen is safe (based on the number of DLTs) and subsequent dose de-escalation, and staggering enrollment of the first three patients by a minimum of 21 days to ensure that an acceptable safety/toxicity profile for each patient is established.

The language in the consent materials for the planned dose versus the lower dose refers to situations in which the GMP manufacturing of the CART-meso or CART19 cell products fails to reach the target dose but the CART products pass the established release criteria. In this situation, the patients have the option of receiving a lower-than-planned dose of CART cells. These subjects will still be required to follow all study visits and will be included in the safety analysis but not the efficacy analysis. The following clarifying language will be included in the ICD: "If the planned study dose cannot be made due to manufacturing or technical issues, the study physicians may still recommend giving you the lower T-cell dose that has been made, if they feel it is safe and poses no additional risk to you. If you receive a T-cell dose that is lower than the planned study dose, you will still be required to undergo the same schedule of visits and procedures as participants who receive the planned study dose. This is because the safety of the study treatment, even at the lower doses, still needs to be closely monitored. If you choose not to receive the lower T-cell dose, you will no longer be able to participate in this research study."

In response to the reviewers' comments regarding the persistence of CART-meso cells, the investigators noted that given their preliminary data documenting rejection of CART-meso cells in all patients and that the CART-meso construct includes a murine scFv, it is very unlikely that CART-meso cells will be persistent. However, the investigators agreed to revise the consent language to clarify that withdrawal from the study is not encouraged, due to the possibility that CART-meso-19 cells may persist indefinitely in the body. The consent will clarify that voluntary withdrawal means withdrawal from clinical monitoring that will assess the patient's health and follow the persistence of these cells in the body. The following language was proposed: "You can decide to stop at any time; however, it is important to recognize that CART-meso-19 cells may persist indefinitely in your body, cannot be removed, and may possibly cause delayed side effects. Therefore, we strongly encourage you to continue being followed by your treating physician, who will continue to monitor your health and the persistence of CART-meso-19 cells in your body over time."

The investigators also proposed amending the ICD to say, "It is not known whether participation in this research study will benefit you or be effective in treating your pancreatic cancer," rather than, "You may not get any benefit from being in this research study," in discussing anticipated benefit.

A list of medical terms (including apheresis) and their definition in lay language has been added to the end of the informed consent document and was submitted with the response to the reviewers' comments.

The investigators agreed with the other recommendations regarding the ICD and have modified the proposed consent document accordingly.

2. Responses to RAC Discussion Questions

Dr. Ko noted that the UPenn study is currently open and accruing new subjects and that the proposed trial and the UPenn study will be run in parallel. Results of these and other trials are likely to inform ongoing clinical research. Dr. Ko and Dr. June, an investigator on the study, provided several lines of evidence regarding persistence and off-target effects. The team's experience suggests that CART19 appears to have greater efficacy than rituximab with respect to durable B-cell depletion. Adult patients treated 4 years ago who have prolonged persistence of the gene modified T cells do not have HAMA. In the pediatric cohort, 75 percent of patients maintain long-term B-cell aplasia; B-cell hematopoiesis is seen in the other 25 percent who lose their CARs.

Dr. June noted that both humoral and cell-based responses with both CART constructs will be monitored in the proposed study. Cell-based responses with CART-meso have not been assessed in prior trials.

Dr. Ko explained that UCSF is a high-volume tertiary referral site that primarily serves previously treated patients. Given the multiple and often overlapping studies that may be open to patients with a specific disease, there may be some patients and trials that are better matches because of the eligibility criteria. Each individual patient, however, is informed about the entire array of studies that are open. The investigators strive to avoid any bias in terms of steering patients toward one protocol over another.

The investigators will address the additional recommendations for the ICD.

E. Public Comment

No comments from the public were offered.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

Preclinical Issues

- The anti-mesothelin scFv (single-chain variable fragment) in the CART-meso is of mouse origin and therefore potentially immunogenic. In subjects dosed on your previous CART-meso trial, the CART-meso cells failed to persist and you documented the development of human anti-mouse antibodies (HAMA). The rationale for co-administering CART19 is the hypothesis that CART19 T cells may induce humoral tolerance to the potentially immunogenic CART-meso by depleting B cells. While you have documented the development of HAMA, it would be helpful to determine whether there was also a HAMA-specific T cell response, as such a response would not be affected by depletion of B cells.

Clinical and Trial Design Issues

- Elimination of B cells could also be accomplished through the use of licensed antibodies, such as the anti-CD20 antibody, rituximab. You stated that rituximab would not be as effective in inducing humoral tolerance, citing data from studies that showed that rituximab failed to eliminate anti-alphaGal antibody production in a non-human primate model and prevent the development of neutralizing antibodies against the immunotoxin LMB-1 in a small study of five human subjects. In addition, you cite data in a murine model that rituximab does not eliminate B regulatory cells.

Despite these data it may be helpful to establish that the CART19 cells are more effective than rituximab in this clinical setting. The effect of rituximab on the persistence of the CART-meso cells could be evaluated by adding a rituximab cohort to the ongoing study of CART-meso cells in mesothelin-expressing cancers (NIH OBA Protocol # 1311-1277), or by considering a rituximab cohort for this study.

Ethical, Legal, and Social Issues

- The statement in the informed consent document regarding the potential benefit of enrollment in the trial has been revised to state “it is not known if participation in this research study will benefit you or be effective in treating your pancreatic cancer.” This statement could be interpreted optimistically to mean that although it is not yet known, there could be the potential for significant benefit. While there have been some very impressive clinical results in early phase trials using CART19 cells against hematologic malignancies, this approach is quite different. Consider changing this to a statement that direct clinical benefit is unlikely in a Phase I trial such as this, which is primarily designed to test safety and feasibility. Such a statement may be less prone to therapeutic misconception, especially as this trial will recruit individuals with no other therapeutic options.
- The informed consent document (ICD) tries to explain the potential impact of developing HAMA by noting that enrollment in this trial may preclude use of therapies that are derived from mouse antibodies. It may be helpful to provide some examples of approved therapies that may not be available in the future because of the development of -HAMA..
- The ICD states that if the target dose of CART19 and CART-meso is not reached, subjects will have the option to undergo a second leukapheresis for a second manufacturing process. Subjects also have the option to receive a lower than target dose, if the subject cannot or is not willing to perform a second apheresis, or if the second manufacturing process fails. Regarding this option, the ICD states that the study physicians “may still recommend giving you the lower T-cell dose that has been made.” The term “recommend” can be misconstrued as implying that the investigator is recommending this dose as a treatment. Consider replacing “recommend” with a more therapeutically neutral word, such as “made available.” In addition, subjects who receive a lower dose than planned by the study should be informed how their data will, or will not be used, to inform this research project.

G. Committee Motion 2

Dr. Kohn summarized the RAC recommendations to be included in the letter to the investigators, expressing the comments and concerns of the RAC. Dr. Kohn requested a vote, and the RAC approved these summarized recommendations by a vote of 12 in favor, 0 opposed, 0 abstentions, and 0 recusals.

VI. RAC Bioethics Discussion

A. Welcome and Introductions

Dr. Kohn opened the second half of the meeting, which included a series of bioethics discussions of issues encountered with early phase first-in-human gene transfer trials, including the appropriateness of enrolling young pediatric patients in trials for diseases that also affect adults and older children, considerations for obtaining assent, and how best to communicate risks and benefits of participation as well as issues relating to long-term follow-up and reproduction in trials for patients with end-stage disease, in particular cancer. The case studies and questions posed for these sessions were developed based on extensive discussions over time by the RAC. Lead discussants for each session framed the issues from their perspective, followed by general discussions that were open to all present. Reference materials including several articles and the current *NIH Guidance on Informed Consent for Human Gene Transfer Trials* were provided to attendees. The ultimate goal of these sessions is to provide a framework to allow the RAC and investigators to work through similar cases in the future, to assist investigators and institutional review boards (IRBs) in the design and review of trials, to assist investigators and IRBs in the design and review of trials, and to determine whether updates to the existing guidances are warranted.

Dr. Kohn welcomed those in attendance, including RAC members and guests, who introduced themselves by name, affiliation, and research interests.

VII. Bioethics Discussion Session I(a): Balancing Access to Clinical Research for Pediatric Patients with Ethical Standards in Early Phase Gene Transfer Trials

Session I(a) included three presentations, a case study, and a discussion involving RAC members, the speakers and panelists, and other guests.

A. Presentation: Regulations Governing Enrollment of Pediatric Patients into Research Trials that Pose “Greater than Minimal Risk”

Speaker: Kristina Borrer, Ph.D., Office for Human Research Protections (OHRP), NIH, Rockville, MD

The Department of Health and Human Services' (HHS) basic regulations for the protection of human research subjects are found at Subpart A, often referred to as the "Common Rule" because the regulations are shared by many different Federal departments and agencies. Subpart A includes some discussion about inclusion of children and other vulnerable populations to ensure that selection of subjects is equitable (per 45 *Code of Federal Regulations (CFR)* 46.111(a)(3)) and that the IRBs, when reviewing protocols involving such populations, take into account these additional considerations and protections. Subpart D has additional protections for research involving children. One of the criteria for approval of research involving vulnerable subjects is that additional safeguards will be put into place to protect those subjects, including children (45 *CFR* 46.111(b)).

"Children" are defined as persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted (45 *CFR* 46.402(a)). Legal determinations in these cases (e.g., age of consent) are based on laws under the local jurisdiction, which usually refers to the state, and are therefore not Federal determinations. Because children cannot consent for themselves, research involving children requires provisions for parental permission, which is similar to consent for adults, as described in Subpart A section 116. For minimal risk research or research with prospect of direct benefit, the IRB may allow permission from one parent. For greater-than-minimal-risk research without direct benefit, permission from both parents is required (45 *CFR* 46.408(b)). The regulations allow for consent or permission to be altered or waived in the same way the consent may be altered or waived under Subpart A; a waiver requires that the research must not involve more than minimal risk, the rights and welfare of subjects must not be adversely affected by the waiver, the research is not practicable without the waiver or alteration, and, when appropriate, subjects will be informed about their participation afterwards. Provisions within Subpart D allow for waiver of parental permission if obtaining consent is not a reasonable requirement, such as if the child is neglected or abused. Dr. Borrer noted that gene transfer trials will rarely meet the criteria for a waiver or alteration under either Subpart A or D.

In addition to parental permission, there should include adequate provisions for assent for research involving children. Assent is an affirmative agreement; mere failure to object should not be construed as assent (per 45 *CFR* 46.402(b)). IRBs will usually require assent when it is determined that children enrolled in a study are capable of assenting based on age, developmental status, and cognitive ability. The IRB can waive assent in situations even if the children are capable of assenting (e.g., those who are older and do not have any cognitive problems) where, for example, the research has the prospect of direct benefit to the subjects and this benefit is not available outside the research context. Dr. Borrer pointed out that, unlike consent and parental permission, the regulations do not state what elements of assent are required. The regulations also do not require documentation of assent. IRBs therefore have considerable flexibility as far as what they can approve for an assent process. A one-size-fits-all approach to assent is not recommended given the considerable differences in intellectual and emotional capacity and maturity among children. Assent for younger children will probably look much different than for older children, while for some adolescents, assent may closely resemble consent.

All research must meet the requirements under Subpart A for criteria for approval, including that risks to subjects are minimized, that risks are reasonable in relation to anticipated benefits, and that subject selection is equitable. There are four basic categories of research involving children that can be approved. Category 1 is research that involves no greater than minimal risk (45 *CFR* 46.404), which the IRB can approve with ensuring that adequate provisions for assent and parental permission are in place; there are no special requirements except for parental permission and assent, which can be waived or altered under certain circumstances, as noted above. Category 2 is research that involves greater than minimal risk but with prospect of direct benefit to the individual subject (45 *CFR* 46.405). For Category 2, adequate provisions for assent and parental permission must be in place, the risk to the subjects has to be justified in relation to the anticipated benefits, and the risk and benefit profile must be at least as favorable to the subjects as available alternatives to participants. Category 3 is research that involves greater than minimal risk—but not more than a minor increment over minimal risk—but with no prospect of direct benefit (45 *CFR* 46.406). For Category 3, the intervention or the procedure that participants undergo must be reasonably commensurate with actual or expected experiences (i.e., routine medical or dental visits), and the research has to be likely to gain generalizable knowledge either about the child's disorder or condition to better understand or ameliorate that disorder or condition. Category 4 is research that is not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 *CFR* 46.407). Category 4 studies involve greater than minimal risk with no prospect of direct benefit and require additional levels of approval beyond the IRB. Such research must be reviewed by a Secretarial panel and appointed experts and can be approved only if it meets sound ethical principles. For both 406 and 407, permission is required by both parents or guardians unless one parent is not reasonably available or does not share custody. Special provisions are in place for wards of the state, who can be enrolled in a Category 3 or 4 study only if the research is related to their status as wards or is conducted in settings in which the majority of subjects are not wards. In addition, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child (45 *CFR* 46.409).

Dr. Borrer also commented on the component analysis, which allows the IRB to assess the risks and benefits of different arms of a study separately. This concept is particularly important in placebo-controlled trials, which potentially might otherwise not be approvable if the overall risks of the study are greater than greater than minimal and more than a minor increase over minimal. With component analysis, however, for the children in the placebo-controlled arm, there is no prospect of direct benefit, but there is also a minimal risk in certain circumstances, which could be approved under 404. Dr. Borrer noted that both FDA and OHRP/NIH have found component analysis to be acceptable.

Dr. Borrer cited several resources for additional information, including the following URL for HHS/OHRP guidance and policy <http://www.hhs.gov/ohrp/policy/index/index.html>.

B. Presentation: FDA Perspective on Enrollment of Pediatric Patients in Early-Phase Gene Transfer Trials

Speaker: Wilson Bryan, M.D., Center for Biologics Evaluation and Research, FDA, Silver Spring, MD

Dr. Bryan highlighted key regulations and issues under Subpart D that the FDA considers in its reviews of first-in-human studies involving children, with a focus on the perspective of the FDA Office of Cellular, Tissue, and Gene Therapies. Similar to the NIH, the FDA generally considers gene therapies as involving more than a minor increase over minimal risk. Per this assessment, studies involving gene therapies fall under 21 *CFR* 50.52, which is analogous to 45 *CFR* 46.405. Under 50.52, clinical investigations involve greater than minimal risk but present the prospect of direct benefit to individual subjects. Thus, a determination needs to be made as to whether a proposed study meets the requirements of Subpart D under 50.52. A parallel question involves whether adults should be studied prior to children. For 50.52, the risks must be justified by the anticipated benefit. Children should only be enrolled in a clinical trial if the scientific and/or public health objective(s) cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults).

Risk evaluation is a complex quantitative and qualitative judgment that is similar to clinical practice. Contextual justification of risk can include the importance of “direct benefit” to subjects, the possibility of avoiding greater harm from disease, justification within the context of disease severity (e.g., degree of disability, life-threatening) and availability of alternative treatments, and having an intervention that has “as good a chance for benefit as the clinical alternatives”. Determination of the level of risk and benefit is based on regulatory definitions of risk. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (21 CFR 56.102(i)). A “benefit” is “direct” if it accrues to individual subjects enrolled in a clinical trial and results from the research intervention being studied (and not from other clinical interventions included in protocol). The word “benefit” is often modified by “clinical” to indicate that “direct benefit” relates to the health of enrolled subject. Prospect of direct benefit is based on the “structure” of an intervention (i.e., dose, duration, method of administration, etc.) and not the investigator’s “intent” or the protocol objectives.

Dr. Bryan acknowledged the range of perspectives regarding what constitutes a prospect of benefit and noted that there are very vigorous discussions regarding this issue within his team, which typically includes a team leader (e.g., a Branch Chief), a primary clinical reviewer, pediatric ethicists, and sometimes the Office Director. The reviewers consider all available evidence in assessing risk and benefit, including results of *in vitro* studies, pharmacokinetics and biodistribution, and animal models. Several factors, including sample size, reproducibility of findings, and efficacy of animal models, are weighed in determining whether or not the research involves prospect of benefit. Because these factors are weighed differently by members of the team, assessment of benefit requires empirical evidence, not solely a rationale for potential direct benefit. The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design to maximize the contribution and predictive value of the resulting data for clinical safety and therapeutic activity. Recommendations for preclinical testing are provided in the reference document, *Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products*.

If the research is determined to involve prospect of benefit, the next question is whether the prospect of benefit or the anticipated benefit sufficient to justify the risks. In weighing this question, the reviewers consider whether the risk:benefit ratio is at least as favorable as the available alternatives. If the team decides that the prospect of benefit is not sufficient to meet that threshold, then studies in adults may need to be conducted first to gather additional evidence of prospect of benefit or reduced risk to determine whether the balance goes more toward benefit to address the Subpart D requirements. Recommending that studies should be conducted in adults first raises further questions, including whether there is a relevant adult population that is feasible and ethical for a study in which the primary objective is to gather preliminary evidence of safety. The FDA team often meets with sponsors to make their argument about risks versus benefits and state how their proposed study will meet the requirements of Subpart D, including whether the research could be feasibly conducted in any adult populations without unnecessarily exposing subjects to risk. If the team determines that a specific study in adults is not feasible or that the risks for an adult population are unreasonable, then that study could not be done.

C. Presentation: A Bioethicist and IRB Chair’s Perspective

Speaker: Norman Fost, M.D., MPH, University of Wisconsin, Madison, WI

Dr. Fost opened his presentation by commenting that the basic ethical problems in pediatric research are that research is not clinical care and that, while there may be benefit to patients in some research studies, the goal of research is not to benefit the patient. In their role as investigators, clinicians are not acting as physicians (or other clinical practitioners) but as scientists. Dr. Fost does not question investigators’ deep concern for their patients, but he pointed out that investigators are involved in activities that clinicians taking care of patients do not ordinarily do, such as randomizing a patient to an intervention and following a dose-escalation plan for which some patients may receive doses that are too low to produce a clinical effect while other patients may receive doses that result in adverse effects. In addition, clinicians do not typically shield their patients from interim data.

Consent is the alleged buffer that protects the research subject from unwanted intrusions and from being an unwilling volunteer in the advancement of knowledge gained through research protocols. Consent documents state that patients will be provided information that might affect their willingness to join or stay in a study. Dr. Fost commented that in reality, this language is misleading. For example, studies have confidential independent data and safety monitoring boards (DSMBs) that, perhaps for good reasons, keep the patient from access to information that they would likely want to have. He noted further that such provisions are in place because the dual loyalty to the current patient versus future patients often tilts toward the scientific goals of the research and favors the larger good of possible benefit to future patients.

Cumulative evidence from the past 50 years suggests that consent is often ineffective in adults and is usually ineffective in children because children cannot meaningfully consent at any age. Dr. Fost also referred to recent empiric data from Dr. Kodish and his colleague show that during consent transactions, the investigator spends very little time talking to or interacting with either the parent or child or trying to assess true interest in joining the study. Prior research by Dr. Rossi and colleagues found that young children's and adolescent's feelings about participating in research studies were very different from recruitment rates for these groups. These issues are especially problematic and raise ethical concerns in no-benefit studies when the research involves minimal risk (e.g., needle sticks), where the utility of a research procedure does not justify the risk. Dr. Fost noted the inconsistency in finding it intolerable to stick an adult with a needle without his or her consent but considering the same procedure acceptable for children, who are vulnerable and cannot provide consent or give their permission in any meaningful way. A similar double standard exists, for example, with respect to laws regarding corporal punishment. The justification for this double standard has been that the research or procedure has utility and advances the interests of children as a whole while requiring sacrifice by some the interest of future children. Dr. Fost posed the question that, if this is a good enough argument for children, why isn't the same argument applicable to adults? If consent were not required of adult research subjects, couldn't knowledge be advanced more quickly in the interest of adults in the future?

Phase I trials are not of zero benefit, but they are at the very low end of likely benefit. Cumulative data suggest that less than 5 percent of Phase I studies accrue medical benefit to individual subjects, and gene therapy trials are at the low end of that low end. Recent data indicate that selected studies may have much more substantial benefit, 50 percent in some trials. In general, however, based on data from the prior two to three decades, the probability that the child is going to benefit from participation in a Phase I trial is extremely low. Dr. Fost added that further consideration should be given to the meaning of benefit within the context of the age of the patient. Just as children are not small adults, infants are not small children. Whether there is benefit with participation in a Phase I trial differs for a 5-month-old compared to a 5-year-old or a 10-year-old. Adults and older children have hopes, dreams, aspirations, activities to do and look forward to, plans for the future, and even if they're dying, people to say goodbye to. In contrast, infants and very young children do not have these same qualities. Living another few weeks or months can be profoundly important and meaningful to a parent and can also be very important to a 5- or 10-year-old. However, such an outcome is unlikely important from the individual perspective of a seriously ill 5-month-old or a severely cognitively impaired 5-year-old whose understanding is limited to the present and who only knows the benefits and burdens of the current day or the next few hours. Curing a fatal illness, which is rare in a Phase I trial, can have major benefits to a 5-month-old, but the benefit of extending life for 3 to 6 months is unclear, particularly for a child who is not able to comprehend what he or she is going through and who has a lot of suffering.

Consent and assent are supposed to be the mechanisms for protecting children from unwelcome or unwanted intrusions. The word "consent" literally means to "think with," and it is something the patient, or arguably his or her representative does, not the investigator. Thus, statements such as "The investigator consented the patient" are not accurate. For consent to be morally meaningful, Dr. Fost commented, there has to be some reasonable understanding as to what participation entails and what alternatives are available. Evidence suggests, however, that messages from the investigator do not correspond well with the messages received. Because comprehension is rarely assessed, there is no basis for claiming that the patient, whether an adult or a child, has consented or given their permission. A signed consent form does not reflect whether the patient read or understands the information in the document or whether the

patient consented; its purpose is to protect the investigator from liability. With respect to children, a parent cannot consent in any meaningful way for a child. All the parent can do is to provide legally acceptable permission to protect the investigator. Understandably, parents of a child who is suffering or dying often choose anything that might alleviate the child's pain or prolong the child's life even a short amount of time. Because of such situations, however, the parent is not an ideal surrogate because of his or her conflict of interest.

The purpose of assent is to provide an added layer of protection against unwanted volunteerism from a child who might not want to be in a study. Dr. Fost commented that assent in the real world does not appear to be taken very seriously. Further, it is not clear that information about the optional nature of participation is disclosed to the child, even if he or she is old enough to understand. Dr. Fost also did not find the rationale for restricting the opportunity to say no to children over the age of 7 to be clear. He noted that lack of language does not preclude the investigator or parent from knowing a child's preferences. Even among very young children and infants, dissent is not always in doubt. For example, few 3-year-olds would want a non-therapeutic needle stick and even fewer would likely want to undergo a lumbar puncture. A child's objections can be overridden when there is a clear medical benefit and favorable risk:benefit ratio for an intervention, such as an appendectomy or vaccination. If an intervention and participation in a Phase I trial are truly optional, no one would question or consider a parent neglectful by not wanting his or her child to undergo a certain procedure or enroll in an early-stage protocol. However, in the research setting, a child's preferences are often overridden, and not for paternalistic reasons but for the benefit of future patients.

Dr. Fost relayed his observations on what can happen when emotion is injected into review and decision-making processes. In addition to the moral dilemma as to whether it is ethically justified to expose an ill child to an intervention that is not likely to be medically beneficial, investigators and review boards such as the RAC face parents of a dying or suffering child who are pleading for help. While it would be insensitive to not consider these pleas or rigorously discuss how to proceed, Dr. Fost noted that when parents and children enter the room, positions can shift, candid and critical discussion stops, and voting by the committee can be impacted. He acknowledged that the patients' views are important and need to be represented but that decision-making can be overwhelmed by the very profound emotions of affected individuals and their families.

Gene therapy deals with very complex, evolving, constantly changing technology. Dr. Fost noted that based on his experience, including membership on the RAC and 31 years as an IRB Chair, there are very few individuals outside the field of gene therapy with the knowledge and capacity to be able to properly review the protocols that come before the RAC. The collective and individual expertise of the RAC members provides an additional layer of protection in the review of gene therapy trials that is not found in local IRBs. Dr. Fost expressed concern that potential changes in the RAC review process that result in returning some or many of these protocols to the local IRBs will remove this layer and the added value of the RAC.

In closing, Dr. Fost stressed that good ethics start with good facts and decisions based on the best available data. The ideal ethical observer considers the interests and perspectives of all stakeholders, has no personal stake in the outcome, is not overcome by emotions when difficult decisions have to be made, and is consistent by deciding similar cases similarly. Dr. Fost acknowledged that data collected in 2014 are not the same as data collected in 2004 or 1994 but added that the prospect of benefit for Phase I studies remains low. Each case is different, however, and the risk of new agents will vary depending on the available alternatives and whether there is evidence with similar molecules or entities.

Discussion

Dr. Zoloth asked Dr. Fost at what point he would reconsider his perspective on the low efficacy rate of Phase I clinical trials. Dr. Fost replied that the science does not currently support a change in the 3 to 5 percent starting position and that any re-assessment involves case-by-case evaluations. For example, CAR agents in some studies have shown a 50-percent response, indicating meaningful benefit even in children. Whether those same agents or a slightly different form of those agents have a similar effect in

other diseases has not been studied yet. The prospect of benefit for those agents in other settings is therefore not clear, and results of selected studies do not change the proportion of Phase I trials showing direct benefit. Dr. Kohn noted that efficacy may be demonstrated for a specific agent and target (e.g., a CAR to treat leukemia) and that a shift may come with demonstrating efficacy with a class of compounds or agents (e.g., CARs). Dr. Kiem commented that improved outcomes in early-phase studies are not limited to CAR cell therapies but that it is not clear how to classify studies that have a higher likelihood of some efficacy and benefit than the “classic” Phase I trial.

Dr. Ross asked Dr. Bryan to clarify why the FDA team would review and potentially approve a first-in-human Phase I gene transfer trial under the equivalent of 405 and not 406. Dr. Bryan explained that from the FDA’s perspective, gene therapies constitute more than a minor increase over minimal risk and that based on this assessment, such studies could not be approved under 406, which requires that research involves no more than a minor increase over minimal risk. The definition of 406 also states that the research have no prospect of direct benefit, while 405 requires prospect of direct benefit. Dr. Ross questioned the assumption that Phase I gene transfer trials involve the prospect of direct benefit, especially studies of novel first-in-human agents, and asked whether such studies should be reviewed under 407 or require an added level of review beyond the local IRB (e.g., the RAC). Dr. Bryan noted that the FDA considers these products to have the prospect of direct benefit and, as such, they fit under 50.52. He recognized the differences in perspectives regarding this determination, including within his agency, but added that, per his presentation, the team considers a broad array of data in assessing risk and benefit, including *in vitro* data, animal data, and data from related products.

D. Case Study 1

Panelists: Crystal Mackall, M.D., National Cancer Center (NCI), NIH, Bethesda, MD
David Maloney, M.D. Fred Hutchinson Cancer Center, Seattle, WA
Melinda Merchant, M.D., NCI, NIH, Bethesda, MD
Catherine Bollard, M.D., M.B.Ch.B., Children’s National Health System, Washington, DC

Dr. Kohn presented the first case study and questions for review and discussion:

Case study: Several Phase I T-cell immunotherapy protocols have shown significant efficacy (more than 50 percent response) in children with advanced cancer who have no other therapeutic options. Children at this stage of their disease have a very limited life expectancy. This approach has been less successful in adults with the same disease, and more toxicity was seen in adults than in children. Nonetheless, there have been serious toxicities in both children and adults. A new protocol will target the same hematologic cancer for which previous T-cell immunotherapy protocols have demonstrated significant clinical benefit for children; however, the target antigen for the gene modified T cells was changed. The design of the trial, including dosing, draws on the experience of previous protocols. Additionally, the preclinical data are as strong as what was seen in these other trials. The investigators propose to enroll children in this trial.

The following questions were posed for this case study:

- Is it necessary to enroll adults first?
- Should older children be preferentially enrolled over younger children?
- How should assent be obtained if older children are enrolled?

E. Discussion

RAC members opened the discussion, which continued with questions and comments from the panelists and other guests in attendance.

Dr. Mackall noted that, as a pediatric oncologist who conducts clinical trials, her goal is patient benefit as defined in 45 CFR 46.405; that is, research with the prospect of direct benefit for the individual child-participant. Thus, any trial that is designed as a dose-finding or feasibility study would not be appropriate for enrollment of children. This approach can present a conundrum with respect to some Phase I trials, which are designed primarily to test safety not efficacy. Given this information, and the overall historical

response rate for Phase I studies, investigators need to be careful to not overstate the benefit of participation, thereby creating false hope. Dr. Maloney noted, however, that many early-phase studies no longer fit the “classic” definition of a Phase I trial with safety as the primary objective and also include testing a targeted intervention for efficacy. As soon as the study cohort is selected based on the target expression for the intervention, then the risk:benefit ratio is altered in favor of the patients. Per this rationale, for the case study above, there is potential for direct benefit assuming that the selected population carries the target. Dr. Merchant agreed that there has been a shift in the nature of the research and that there now are more Phase I/II trials than pure Phase I studies. This does not mean that a study will offer direct benefit, but potential for benefit should be taken into account based on available evidence and disease status. Professor Dresser acknowledged the history of Phase I trials and the low rate of benefit with such studies but questioned whether, with newer targeted interventions, early-phase gene transfer studies may offer potential for direct benefit. She also noted that there can be a distinction between “benefit” to the patient (e.g., improved quality of life) and “scientific benefit” (e.g., decreased tumor size) and suggested tracking these types of benefit in studies in both children and adults.

Dr. Mackall commented on how much the field of clinical research on childhood cancer has evolved over the last 25 years and how ethical issues and positions involving participation of minors in clinical trials remain a moving target that need to be reexamined as the science advances. Historically, pediatric trials would test agents that were anticipated to be effective in adults without clear evidence that the specific drug or product would be applicable in childhood cancer. In that setting, testing an agent in a pediatric population without first testing it in adults was not done. In many cases, however, not enrolling children in clinical trials was considered a missed opportunity to give the patient a potentially beneficial agent. The field has now advanced to where therapies that are specifically targeted to one or another aspect of the cancer cell have been and are being developed, providing the foundation for molecularly targeted gene therapy trials for cancer and other conditions as well. With this progress, agents are being designed for specific subsets of cancer that do not necessarily warrant testing in other disease subsets or patient groups. Dr. Mackall pointed to data showing an increase in the response rate of Phase I trials in pediatric cancer over the past decade, with individual studies showing a complete response rate between 67 percent and 90 percent.

Dr. Donahue pointed out that the historically low response rates in early-phase studies refer to cancer trials, primarily in patients who had failed conventional therapies, and that the approximate 4-percent response rate was an improvement compared to the patients’ previous lack of response; within this context, the response suggests potential benefit. He questioned the adequacy of this information as the standard for assessing risk and benefit of current research trials not only for cancer drugs but in particular for other agents and diseases. Dr. Donahue also challenged arguments against use of the word “therapy” for proposed interventions by noting that the power attributed to therapy, that is, the expectation of absolute good and no harm, is not accurate. This is clearly demonstrated through multiple examples of established treatments that have failed and caused damage, including death, as cited by Dr. Fost (e.g., bicarbonate therapy for respiratory acidosis, exchange transfusions on otherwise healthy children with elevated bilirubin but no hemolytic disease). Thus, to hold experimental interventions to a standard that many established therapies do not meet adds confusion and may prevent the use of terms that patients understand for reasons that are not valid.

Dr. Kohn commented that the RAC has struggled with these issues, including how to define “first-in-human” use and how to evaluate potential benefit for such studies. For example, if a protocol involves a cDNA for an eye disease that has not previously been administered but the vector has been well characterized and studied, does that constitute a novel first-use application and pose new risks to subjects? Dr. Merchant noted that the NCI IRB has reviewed protocols involving agents previously tested in adults that have been slightly modified and that were being newly tested in both pediatric and adult patients. In these cases, the IRB has evaluated the aspects of the interventions that are new and used that information in assessing risk and benefit. For first-in-human trials, assessment of risk and benefit and decisions as to whether and how to proceed are based on the disease of interest and the strength of preclinical data, specifically how translatable and predictive such data are estimated to be. Some preclinical models can give good signals for both the target of an intervention and potential toxicities. Dr.

Nelson recalled a protocol reviewed by the RAC several years ago in which, as the bioethicist supporting Children's Hospital in Philadelphia, he recommended studying children first based on animal data showing 100 percent efficacy in the dog model and 70 percent in the mouse model. Three adults were enrolled first in that protocol, and subsequent testing showed improvement in all three children who participated in the trial. Dr. Kohn cited an opposite example for the drug thalidomide; in this instance, the animal model did not predict serious toxicity in humans because mice do not have the enzyme that makes the drug toxic.

Because there is no *a priori* way of knowing what the results in humans are going to be, how an agent will act is one of the unknowns going into a first-in-human trial. As the field advances and investigators gain more experience and knowledge as to the mechanisms of action of these agents and their impact on risk, it may be possible to take a broader view of early gene transfer trials instead of looking at each molecule individually. Dr. Merchant expressed hope that, for example, for the field of oncology, the research will continue to progress so that agents and trials will be designed to target the molecular and epigenetic targets of pediatric cancers that are distinct from adult cancers and studies.

Dr. Kodish noted that the work he and his colleagues have done on informed consent suggests that prospect of direct benefit for Phase I protocols may be as low as 1 percent. Dr. Ross added that Phase I studies are designed to assess safety as the primary outcome and agreed that available data show the prospect of direct benefit for a Phase I gene therapy trial to be very low, between 2 and 4 percent.

Dr. Nelson and Dr. Roth-Cline commented that the evaluation of whether a protocol offers prospect of direct benefit is not related to the outcome or the primary hypothesis of the protocol. Rather, it is based on the intervention and a rational study design and whether the trial is optimized (e.g., via choice of dose and duration of dosing) to provide the child the possibility of benefit. At times, this will seem counterintuitive because a higher dose that may involve greater risk may be tested. Making such a decision is a complex judgment that depends on several factors, such as disease severity and existing alternatives, similar to the sort of judgment made in the clinical setting.

Another question raised was whether it is ethical to wait years for outcomes in adults to test an agent in children with a fatal or severely debilitating disease. Federal regulations require subject selection in a clinical research trial to be equitable unless there is a compelling scientific or safety reason to exclude a particular group, including minors. Dr. Bollard commented that, particularly for diseases that are highly prevalent in children, equal access to research studies means inclusion of children. The regulations are designed to protect children, who are considered a vulnerable population. The consequences not only of participation but also of the child's disease, including possible loss of life, quality-of-life (QoL) issues, and how being in a study may affect QoL, need to be considered. Dr. Maloney noted that if there is an opportunity to enroll adults with the target and to collect safety data, the research should proceed accordingly as an added safeguard to protect children from off-target toxicity. The "risk" of excluding minors from a study also needs to be taken into account, however, such as in the case of genetic diseases where patients do not live to adulthood. The challenge is determining the point at which the perceived potential for benefit outweighs some toxicity. Dr. Mackall stated that waiting until drugs are tested in adults translates into approximately 3 years for the whole clinical trial apparatus. For children who have a disease that is being targeted with any of these agents, a delay of 3 years can result in the death of at least some of these children. Dr. Bollard noted the example of some of the CD19 CAR studies in which toxicities in adults have been greater than in children. If such studies are stopped early because of increased toxicities in adults, potential lifesaving treatments in pediatric patients may never be evaluated in children. Dr. Nelson noted that, not including pediatric oncology trials, FDA reviews between one dozen and two dozen first-in-human pediatric protocols each year. In some cases, the basis for the proposed study is limited to the disease of interest and the results of testing in an animal model.

Dr. Fost supported some flexibility in the "adults-first" rule for the reasons stated, particularly with testing of new agents that are targeted to specific antigens of tumors of greater relevance to children (e.g., Wilms tumors). Reconsideration of the adults-first rule may also be warranted given evidence that studies are

increasingly showing that the toxicity of newer targeted agents is less than toxicity with chemotherapy and products that do not target specific tissues or cells and have a systemic effect. Dr. Bollard recommended opening trials up to children if the disease is highly prevalent for pediatric patients and if results of Phase I trials are trending toward improved response rates. Investigators and sponsors should not be deterred from bringing a new agent to trial, even with the many filters preceding the implementation of Phase I studies, including funding, time, and institutional and agency approvals. On the other hand, Dr. Fost noted, confidence in a specific genetic intervention may need to be tempered given cumulative historical data that 95 percent of the time, an agent does not work.

Dr. Zoloth expressed cautious optimism about the “potential benefit” of gene therapies but recognized the inherent conflict of interest of emotionally engaged and perhaps desperate parents and enthusiastic and compassionate physicians. She supports having an independent party or parties involved in discussions not only with patients and family members but also with oversight committees such as the RAC to provide balance, consistency, and restraint to the conversation. Attendees appreciated these comments and suggestions and recognized that support for a specific intervention may be viewed as overly enthusiastic. However, several attendees also pointed to the dozens of calls they receive each week from parents whose child or children they cannot help. Dr. Kodish added that parents whose child has died after participating in a clinical trial may not necessarily have the view that the intervention or the study was a failure. Instead, some are able to construct meaning from the experience in terms of helping other children. Whatever the outcome or the parents’ views, lessons can be learned from parents at all points in the research process, whether it is after their child’s participation or through comments presented to the RAC when their children are desperately ill. Determining when and whether to include or exclude children in research protocol requires careful consideration of multiple factors. Dr. Merchant noted the complexity of gene transfer research and cautioned against making a blanket assessment that all Phase I trials have a very low chance of benefit. Ultimately, each agent may need to be reviewed on a case-by-case basis as to potential benefit and appropriateness to test in children, including decisions regarding enrollment of older children before proceeding to enrollment of younger children. Investigators and review boards may wish to bring in *ad hoc* experts to provide guidance in making these determinations.

As noted in Dr. Borrer’s presentation, current regulations do not require documentation of assent. However, protocols should have a process that clearly describes the study to children and their parents, including the potential risks and benefits and any available alternatives, including other trials. Studies that enroll pediatric patients should also include a process for obtaining dissent. The age and stage of development of the child are critical to helping the child understand any complex issues of the research, and a plan to assess the child’s developmental state should be considered. Older children, if capable, are given a voice in how they can express their degree of risk tolerance and the uncertainty that they’re willing to tolerate. Dr. Nelson noted that in his experience, those who can provide the best assessment for themselves are the children (and parents) who have already gone through an acute emotional situation involving their disease and have had time reflect on that experience. A parent can attest for a younger child or an older child who has diminished capacity. Dr. Maloney commented that in cases where the child is facing a life-threatening illness and has no other real options, assent should be waived and the parent(s) should make decisions on behalf of the child.

Attendees did not agree on the question of whether a child can truly decline or agree to a study procedure or to participate in a protocol. An independent advocate for the child may be part of both the assent and dissent processes to assist in assessing the child’s preferences and level of understanding what is entailed in a study, including the study’s risks and benefits. Dr. Merchant noted that the Children’s Oncology Group (COG) provides guiding principles to inform practice regarding assent and dissent. These principles will sometimes be in conflict with each other, but the COG has a set of very clear recommendations about waiving assent, documenting assent, and resolving disagreements with children about research participation. Dr. Kodish was involved in developing the COG bioethics recommendations and noted that they talked about respect for children in homage to the Belmont principle of respect for persons. He mentioned that they were inspired by Myra Bluebond-Langner’s work on mutual pretense. With these principles in mind, the COG was careful to use language that refers to parental authority rather than parental autonomy. Dr. Merchant expanded on these points and identified three of the COG’s principles for further consideration. First, investigators should always respect children as persons and,

together with parents, should honor children's developmental autonomy in decisions about research participation. Second, investigators should respect parents' role in guiding their children's moral development and assessing their children's best interest. Third, policies regarding assent as well as IRB's decisions with respect to particular protocols should be sufficiently flexible to accommodate the wide range of medical, psychological, and contextual circumstances seen in pediatric oncology.

Dr. Bollard and Dr. Merchant pointed out that consent and assent are more than simply having a patient or parent sign a document and involve ongoing discussions that continue over the course of participation in a trial. Dr. Merchant noted the rigorous discussions by the NCI IRB regarding how the consent process should be done and whether an assent document is needed for an individual pediatric trial. NCI consent documents include a signature page that, when applicable, the parent signs and says, "My child has been explained this study, given a chance to answer questions, and has given their assent, and I will sign here attesting to that." For NCI studies, the PI responsible for the consent/assent process and for delineating the process in the protocol submitted for review by the NCI IRB. Dr. Merchant has older patients in her practice sign the consent document even though their signature is not legally binding. The aim of this approach is to include children in the discussion as much as possible, not only to help them understand what is entailed in the trial but also to let them know that they are part of the research process.

Dr. Merchant noted that dissent and situations in which the child and parents fundamentally disagree about research participation are rare. In most cases, decisions by the parents and child are usually in alignment. In cases when differences have arisen, Dr. Merchant has involved bioethicists and used separate sessions to try to understand the root of the disagreement and where the issue falls on the continuum for the particular patient. Other factors including the cognitive ability of the child and the parents' position are taken into account when considering the child's dissent. Dr. Nelson added that in his experience with oncologists, a study or procedure is typically not done unless the child agrees. Dr. Kodish advised keeping the family together, if possible, when discussing differences between a child and his or her parents. The process requires sensitivity, and case-specific ethics consultations can assist in these instances. Dr. Kodish noted that additional support and funding for ethics consultations are needed, especially in settings where cutting edge research is conducted.

Dr. Fost inquired as to possible reasons for the rarity of dissent, which contrasts with the number of adults who decline to participate in Phase I trials for serious diseases. He speculated whether the opt-out rate would be higher if children had a better understanding of the research or if there were better ways to ask children about participation to more clearly discern dissent. Dr. Mackall pointed out that deciding whether to enroll in a Phase I trial involves consideration of a range of factors, including the stage of the child's disease, the impact of any travel on the child and the family, and any additional expenses associated with participation. In addition, it was noted that many children with cancer die before they are actually able to enroll in the study.

Clarification was sought regarding how assent is interpreted, applied, and evaluated. Dr. Fost found the suggestion that children do not need to assent to participate in a research study and that a child's preferences can be overruled, even for Phase I studies, to be highly questionable. In addition, the ages for which such provisions would apply are not clear. Dr. Fost noted his understanding of assent to mean agreeing or affirming or having the right to say no (e.g., per 45 *CFR* 46.402(b)). It is not clear whether other interpretations are consistent with what was intended when the regulations were written or if they represent a departure from prior interpretations. In addition, if there is no process for assent, it is not clear how investigators know what participants understand about a trial. To determine whether meaningful consent or assent is given, it must be studied. Administering a short consent quiz or asking patients for feedback on what the investigator has said during consenting and about the trial or a study procedure can be informative.

Dr. Borrer clarified what the regulations allow regarding ignoring dissent or not getting assent. For children who are capable of assenting, assent must be obtained unless the research involves the prospect of direct benefit that is not available outside of the research or if assent can be waived in the same way that consent can be waived (per 45 *CFR* 46.116(d)). Such waivers are appropriate only for research that is not greater than minimal risk, which eliminates most gene transfer trials. Dr. Nelson

questioned whether a more nuanced discussion of the ethics of a waiver for assent under the regulations is needed. He noted that gene transfer at this point is not available outside the research setting, thereby meeting one of the criteria for a waiver. If a trial is also assessed as having potential for direct benefit, does this mean that the automatic response is to request a waiver? In response, Dr. Merchant commented that the aim is not to waive assent in all cases but to make the decision on an individual protocol basis. Dr. Maloney clarified his position by noting that if patients are being targeted for a specific therapy because they have the genetic defect of interest, then an argument can be made for potential for direct benefit, which allows for enrollment of children in a study that otherwise would require approval under 407. If the research also involves an intervention that is the only alternative for a child with, for example, relapsed leukemia, then a request for a waiver could be considered. Ideally, no treatment or procedure would be done without the patient's consent or assent, but parents and children can disagree, which creates a dilemma.

Dr. Merchant questioned whether children's level of understanding tends to be underestimated. Many of the children she and her colleagues see understand that they are participating in research for altruistic reasons and are part of an effort to help other children in the future. Dr. Merchant referred to a study involving pediatric oncology brain tumor patients that showed 95 percent of children between the ages of 7 and 18 understood that they were part of a study and 87 percent understood that they were part of research. The concept of randomization was not as well understood. The first numbers are high and are probably not generalizable to the adult population, but they suggest that physician scientists in pediatric oncology take the issues of communication and consent and assent seriously. Continuing to educate PIs on how to improve the assent and consent process and to assure that patients (and family members) understand that an outcome is not guaranteed is warranted.

Ms. Hardison provided her perspective as an IRB member, a compliance analyst for an academic medical center, and a parent of a child who had many opportunities to be part of clinical trials for most of her life. She commented that the assent forms that she has reviewed over the course of her tenure have not been worded in a way that gives children a chance to say whether or not they agree with what is being done or planned. The assent forms usually simply state what the child can expect to happen. Ms. Hardison continued by noting that parents often do not understand the meaning or purpose of assent; further, many parents do not give their children a choice in these matters. In addition, she pointed out that patients and parents probably do not have the same understanding of direct benefit, particularly in the research setting, as physicians and investigators. However, without awareness of this difference in understanding, it is unlikely that any questions will be asked to clarify what is meant by benefit, consent, or other terms. Dr. Kodish mentioned that he was chairing bioethics in COG when they formulated the guiding principles. He mentioned that they were careful to not use language of parental autonomy instead it was about parental authority, which is a different construct. He mentioned about respect for children in homage to the Belmont principle of respect for persons. He stressed about the importance of keeping a family intact and together if possible. Dr. Kodish also suggested that this kind of research requires a lot of sensitivity and case-specific ethics consultation can be very helpful with that. He mentioned that IRBs' jobs are to protect children and an ethics consultant's job I think is to find common ground in these difficult situations.

F. Public Comment

No comments from the public were offered.

VIII. Bioethics Discussion Session I(b): Balancing Access to Clinical Research for Pediatric Patients with Ethical Standards in Early Phase Gene Transfer Trials

Session I(b) included a case study and a discussion involving RAC members, panelists, and other guests.

A. Case Study 2

Panelists: Victor Santana, M.D., St. Jude Cancer Center, Memphis, TN
Ron Crystal, M.D., Weil Cornell Medical Center, New York, NY
Eric Kodish, M.D., Cleveland Clinic, Cleveland, OH (*via teleconference*)
Steven Hirshfield, M.D., Ph.D., National Institute of Child Health and Development, NIH, Bethesda, MD

Dr. Kohn presented the second case study and questions for review and discussion:

Case study: A gene transfer agent is being developed for a severe progressive neurological disease. Some individuals live into young adulthood, but by then the disease is so advanced that it is not clear that its course can be modified, and many have diminished mental capacity to consent. Similarly, adolescents are often fairly advanced but might be able to assent. This is a rare disease, and it is anticipated that if one receives this gene transfer agent, the expected immune response will preclude redosing. This first-in-human trial is using a vector that has been used before by the same delivery route (intravenous).

The following questions were posed for this case study:

- Would it be appropriate to enroll children before adults?
- Would it be appropriate to enroll younger children (e.g., age 2 years) rather than older, more advanced children, assuming that those older children would be able to assent?
- If the study is to have the prospect of direct benefit, how should the initial dose be selected? Should a dose that shows clinical activity in animals be chosen over a more conservative dose that is less likely to lead to clinical benefit but may be safer?
- How would the analysis change if the delivery of the vector was a first-in-human use (e.g., via intrathecal administration)?

B. Discussion

Dr. Crystal noted the shift in focus from possible public health hazards of gene therapies in the early 1990s to potential benefit of gene therapy trials. For some interventions, evaluation of efficacy (or lack thereof) has been relatively straightforward based on simple phenotype. For successful CAR constructs, leukemia either goes into remission or does not. If a vector carrying the RPE65 gene works, the patient's vision improves. Introduction of the gene for coagulation factor IX either will result in production of factor IX protein and restore function of this protein (e.g., in hemophilia B) or will not. Among the challenges to the field, however, is moving past early-phase trials, which are funded primarily by the NIH and foundations and may or may not demonstrate any potential efficacy, to larger trials that could enable follow-up testing to determine whether an agent is effective. Because of the costs of larger trials, the success or failure of numerous potential gene therapies remains largely untested. With a specific target, some cells are likely to be cured in an early-phase study, which may not be sufficient to be defined as a clinical benefit but suggests a basis of benefit for many of the trials that are conducted.

With respect to the case study above, Dr. Crystal stated that it would be appropriate to enroll children before adults, since it is unlikely that adults would benefit from the intervention, given the description of the neurological disease being studied. He supported enrollment of younger children once initial safety studies done. The lower age limit for enrollment of very young children will be influenced by when children are initially affected, the severity of the condition, and how quickly the disease progresses. The ultimate goal would be to treat individuals before any symptoms develop. Regarding the route of administration, Dr. Crystal commented that he had more concerns with intravenous delivery of gene therapies (compared with intrathecal or other organ-targeted dosing) because of the greater potential for direct response by the immune system. Use of intrathecal delivery would unlikely impact the analysis. In support of comments made during the discussion of the first case study, Dr. Crystal noted that for trials on which he is the PI, several individuals, including a patient advocate, spend time with the patients and families to ensure their understanding of the research and risks of participation, particularly for studies involving fatal diseases and invasive procedures. This approach provides a way to consent subjects effectively and ethically.

Dr. Kodish commented that while the brain is the “organ of consent,” it is important to keep in mind that patients and families often make decisions regarding care and “treatment” with their heart instead of their head. When possible, research should probably be conducted with older children before young children. In the current case study, however, the particular condition is often already in its advanced stages in adolescents, which counters the “age de-escalation” approach. Another example to consider in favor of enrolling younger children involves conditions where end-organ damage occurs the longer a treatment is postponed. Thus, to the extent that there is a prospect of benefit, it makes sense clinically to enroll children earlier rather than later. Regarding dose selection, if sufficient data exist to suggest the prospect of direct benefit, it may be preferable to proceed with less conservative dosing as long as this is clearly explained to the family as part of the consenting process.

Dr. Hirschfield commented that some technical aspects that could inform assessment of risk and guide responses are missing in the description of the hypothetical case study above. For example, it is unknown whether the vector stimulates an immune response or has off-target effects. In addition, the cognitive capacity of the patients at various ages and stages of disease progression are not clearly delineated, which could affect whether the individual can consent (for the young adult) to participate. Capacity could be on a gradient where patients have greater capacity and cognitive ability at the younger age. Dr. Hirschfield endorsed prior comments that enrollment should be limited to patients who have a “measurable” opportunity for benefit, with benefit defined not in terms of an absolute number across studies or patient groups but, for example, whether there is a proof-of-concept model that has shown some correlation of benefit of the planned intervention. For this study case, the investigators should thus consider all comers with adjustments to the eligibility criteria based on the natural history of the disease and available information on use of the intervention. If the trial is first-in-human in terms of the dosing but there is precedent for use of the vector, a low dose or narrow dosing range based on the target cell or tissue should be considered.

Dr. Santana generally agreed with the previous comments and noted the ongoing need to balance doing what is right for the patient, maintain ethical standards, and meet regulatory requirements for research studies. The central tenet of this case is that the clinical condition dictates how to approach the problem. If this is a disease that manifests so that the correction can be done earlier in life and the intervention has the potential to improve the quality of life for children, then there is no reason that the study should not be done in children before adults. Thus, the study should be done at the age at which the patient is most likely to benefit in the course of their disease.

Dr. Santana commented that while assent is an important component, particularly when dealing with innovative experimental therapies, assent itself should not dictate the age for eligibility. In this case, for example, adolescents and teenagers may have some deficit of cognition that could affect their ability to provide assent; the validity of the assent, in turn, could be brought into question.

Addressing the issue of dose in this and similar cases is challenging. For many of the diseases studied in gene therapy trials, the aim is to correct or change the underlying biological behavior to produce clinical benefit, which may be achievable with a minimum effective dose. While results in animals are not always predictive for humans, dose-related biological effects in animals could inform how to define the minimum effective dose, at least to some degree. As for the impact of route of administration on analysis, the study should include the mode of delivery that has the best opportunity for the investigational agent to reach and affect the target organ or cells. If intrathecal delivery meets that criterion for this neurological disease, then the trial should proceed accordingly.

Dr. Chatterjee noted that some diseases have both central nervous system and peripheral sequelae. In such cases, the intravenous dosing route would address the symptoms that the intrathecal route would not, which could be the rationale for use of IV administration of the vector in prior cases. Regarding the age at which dosing should start, there are diseases and family of diseases in which damage occurs early in life and treatments later in life have little to no effect. In these cases, as demonstrated even in animal models, treatment needs to be done early. Dr. Nelson raised the issue of whether useful information could be gained from enrolling the young adults described in the case study, such as safety data. However, enrolling young adults who cannot give consent for the purpose of obtaining safety data to

avoid having to apply the additional protections for children is ethically problematic. Furthermore, under Subpart D, similar protections should be in place for adults (age 18 and up) without consent or decision-making capacity as for children participating in a research study.

Professor Dresser commented that the idea of choosing the original dose based on clinical activity in animals is a departure from the first-in-human safety study, where the dose is often based on the no-observed-adverse-event level (NOAEL) in animals. Such an approach, however, could provide a basis for first-in-human trials designed at least in part to evaluate benefit. Dr. Nelson noted that FDA emphasizes the importance of proof of concept in disease animal models and considers a maximum recommended starting dose, which is lower than the NOAEL. Dr. Hammarskjöld questioned whether this approach represents a shift in starting at a more therapeutic dose as a guiding principle, given the extensive testing and cumulative body of knowledge about all different types of vectors.

Dr. Bryan commented that we really need to think about these trials, not so much as Phase I or Phase II or Phase I/II, but about what the scientific objectives of the trial are. He mentioned that we need to access whether we already have enough safety data so that we can focus about efficacy in this trial. He expressed concern regarding choosing the study population which is most likely to benefit because animal studies can't predict that very well and also determining which population is the best population for the scientific validity of the study. Dr. Santana commented that determining how to proceed is based on what is known about the disease of interest and what the outcome will be. The latter point is especially relevant because the endpoint may be very different for patients with advanced disease versus patients with no or early manifestations of the disease. Consideration of these factors may or may not result in different trials, but as a general principle, these issues should probably be reviewed on a case-by-case basis with a focus on what a study is trying to achieve.

C. Public Comment

No comments from the public were offered.

IX. RAC Bioethics Discussion Session II: Communicating About Risks and Benefits in Early Gene Transfer Trials

Lead Discussants: Norman Fost, M.D., M.P.H., University of Wisconsin, WI
Michael Atkins, M.D., Georgetown Medical Center, Washington, D.C.

Dr. Atkins and Dr. Fost presented the background information and questions posed for this session, which extended the previous discussions and focused on communication of risk and benefit in first-in-human trials in general, the type of language that should be included in a consent form, and how these concepts and language might apply to pediatric trials.

Early phase studies are primarily designed to assess safety. While an individual participant may experience some clinical benefit, data across trials indicate that individual benefit is unlikely in early phase trials. One review of nonpediatric oncology trials from 1991 to 2002 found that for studies testing a single investigational agent, a complete or partial response was seen in less than 5 percent of participants, although a much higher number had stable disease or "less-than-partial" response (Horstmann et al., 2005). It is estimated that more than 90 percent of investigational agents that enter clinical trials will fail to become a licensed product.

The following questions were posed for discussion:

- While each trial is unique, how does one best communicate about the benefits of enrolling in a first-in-human clinical trial?
- Does one need to communicate about the prospect of direct benefit in early phase pediatric trials?

- In addition, as gene transfer agents may persist and have long-term effects, should research participants be advised that enrollment could preclude enrollment in other investigational studies?

A. Discussion

Dr. Fost noted that the data cited above are more than a decade old and there have been many breakthroughs in gene transfer and gene therapy trials since 2002. Cumulative data on these more recent findings are not available, however, which makes it difficult to fully address the issue of how best communicate about the benefits of enrolling in a first-in-human clinical trial, including studies involving pediatric patients. However, presuming that an intervention is “successful” in that it shows a response that eventually leads to a marketable drug, how should this be communicated to patients or parents? Dr. Fost cited the following sample language from the *NIH Guidance on Informed Consent for Human Gene Transfer Trials* to guide the discussion:

“You were asked to be in this study to help the investigators learn more about the type of disease you have. The investigators will try to keep the risks of harm to you from being in the study as low as possible. They believe that being in the study will not keep you from getting any treatments for your disease.”

“This study is experimental. It is meant to investigate the safety, possible harms, and side effects of injecting your cancer with an experimental gene transfer agent called X. This is the first time that this gene transfer agent will be used in humans with your disease.”

“The investigator’s goal is to find out the highest dose of the gene transfer agent that is safe. This is the first step in studying whether it can be used to treat others with your disease in the future.”

Many gene transfer consent forms fail to mention benefit to society. However, potential participants should always be informed that early phase studies are designed for scientific purposes and that those who participate in these studies may extend benefit to future patients by helping to advance scientific and medical knowledge. The investigator should distinguish between these benefits to society and potential benefits, if any, to participants. The following language provides this information:

For protocols enrolling individuals with late-stage terminal disease, the following language has been suggested:

“You have a fatal illness, and while we cannot be certain, other subjects with your condition live [on average < year]. There is nothing that we can offer now to cure you. But scientists are studying your disease and want to ask you to take drugs as an experiment that might someday be used to treat people with a disease like yours. This treatment is in its very early stages. Taking the drug at this stage does not mean that it will help you, for there is only a very rare chance of that happening. The experiment is to test the right dose in people and to see if the drug may be dangerous in people.”

Dr. Fost noted the additional following language that was identified as problematic:

“You have been invited to participate in this study because your disease has progressed despite standard treatment.”

The first four examples are from the NIH guidance document. The additional statement was provided as an example of the type of language not to use in the consent document. Dr. Corrigan-Curay noted that the language is provided to help investigators clearly convey that subjects are participating in a Phase I trial and to portray the likelihood (or absence thereof) of potential for direct benefit to the individual study participant. She added that the NIH language is meant for gene therapy and that the guidance discusses complying with the regulations and assenting children but is somewhat silent on specific language for protocols enrolling pediatric participants.

In recent discussions, the RAC noted that the ICD should clearly state (when applicable) that the study is a first-in-human trial in which the primary objective is to test safety and not efficacy. Use of the phrase

“There *may not* be direct medical benefit to you” implies that there may be a clinical benefit and likely reflects the study team’s optimism. RAC-recommended language included the following:

- “Phase I studies such as this, which are first-in-human studies, *usually do not provide* any medical benefit to subjects.”
- “*Individual clinical benefit is unlikely.*”
- “It is *unusual* for participants in an early safety study to benefit.”
- “This is a safety study, and *no clinical benefit is expected*. The goal is to test for toxicity of this approach and evaluate any potential immune response to this agent.”

Additional revisions to sample NIH language were noted, as follows:

“The gene transfer you get in this study *is not likely to change* the natural course of your disease. This study is not meant to be a treatment for your disease. Instead, the investigators hope that the information learned from this study can benefit patients with [condition] in the future.”

“This study *is not intended to benefit you directly*. Investigators simply want an understanding of gene transfer for [condition]. Information about the amount of DNA needed and the effects of the gene transfer agent will be critical for further studies in the future. Getting the gene transfer in this study will not improve your health or [specific symptoms].”

“The purpose of this study is to test the safety of this gene transfer and to see if we can successfully put the gene into cells of people with [condition]. *Treating your disease is not the purpose of this study*. It is very unlikely that getting the gene transfer in this study will improve your health or [specific symptoms].”

With this background, the discussion was opened to questions and comments.

Dr. Atkins did not agree with premise that data from the *New England Journal of Medicine (NEJM)* publication cited above should be the basis for communicating risk and benefit in early gene transfer trials, given how dated the information is. The analysis in the *NEJM* article does not take into account advances made in the past decade or the current state of the science. The consent process and consent form should be tailored to available information for the specific intervention and/or disease being studied, instead of following strict rules that may or may not be applicable to an individual trial or population. Dr. Atkins commented that for a majority of first-in-human studies, consent language indicating no potential of direct benefit is appropriate. There may be another group of first-in-human trials, however, where data supporting the potential for efficacy is stronger. This latter group may represent many of the pediatric trials being conducted, where the concern among some in the field is that consent language does not accurately reflect this potential. In such cases, participants are not properly informed of the potential benefits of participation, and it would be helpful to have language to better reflect available data. For a subset of trials, consideration should be given to allow for greater flexibility and more optimism in the language in the consent forms. Dr. Kiem agreed, noting that the traditional language of the consent form does not necessarily reflect some recent trials where a level of benefit for the patient is expected.

Dr. Nelson commented that the consent language used to explain benefit does not necessarily need to be connected to the IRB determination of prospect of direct benefit per FDA regulations. Rather, the discussion should focus on whether the language appropriately communicates the facts as would be interpreted by a parent or patient. However, for any study under 50.52, the consent should not say there is a prospect of direct benefit unless clearly merited by the available evidence. Dr. Zoloth stressed the importance of using consent language that is consistent with the proposed research as clearly defined for an early-stage (Phase I) gene transfer trial. If the research does not involve a first-in-human intervention and is based on existing clinical data that suggest potential for direct benefit, then that is not a Phase I trial. Attendees revisited the issue of how to define and whether to re-classify early-phase gene transfer protocols that assess both safety and efficacy (e.g., as Phase I/II trials) and therefore do not match the main objectives of a traditional Phase I study. Dr. Kodish commented that the current classifications appear to be problematic because the one-size-fits-all approach is no longer applicable. Going forward, it

might be preferable to focus on the specifics of the research instead of the broader, general numbered-phase categories.

Dr. Zoloth commented that informed consent is the one opportunity that patients have in the middle of an enormous financial and scientific enterprise to understand what a study and their participation entail. She added that most patients sign up for a Phase I trial for altruistic reasons, not because they expect direct benefit, and this needs to be very clearly reflected and conveyed in the consent document and process. Several attendees were concerned that such an approach might diminish hope for certain patients and interventions and that saying that an agent will not help in any way is misleading. Dr. Maloney agreed with Dr. Zoloth with respect to Phase I trials involving use of gene therapies in individuals without the targeted genetic defect, which have no prospect of direct benefit. However, gene transfer studies involving patients with the genetic defect represent a different category of research that goes beyond simply assessing safety or toxicity. Dr. Zoloth cautioned against using “hope” as part of the justification for assessing or describing benefit of an experimental intervention because it is not part of the structure of a sound clinical trial. She stressed that the job of the physician and investigator is to evaluate the science, offer the best intervention possible, and conduct experiments until a clear outcome is generated. The argument in favor of hope has unfortunately resulted in illogical and at times unethical practices, including lying to patients. Dr. Zoloth argued further against use of the term “treatment” because the agents tested in early-phase studies are experimental and the participants are “subjects” not “patients” in this setting.

In response, Dr. Nelson pointed to the broad differences in how the same or similar terms are interpreted, even among investigators, and underscored the need to take this issue into account in how terms such as “likely,” “rare,” “possible,” “unlikely,” and “treatment” are presented. The challenge is finding the balance between explaining the risks and any benefit of an intervention being testing in a Phase I trial and regulations and policies regarding consent. Dr. Atkins noted that for first-in-human trials, he tries to tell the patient or family as much as is known based on patients treated in similar trials or in the specific trial of interest. Access to data from ongoing multi-site and blinded trials presents additional challenges, both in interpretation of interim data and disclosure.

The discussion returned to the data from the *NEJM* article cited at the start of the session and whether more current data suggest a much higher response rate for gene transfer trials. The investigators in attendance were asked whether most of their gene therapy protocols are likely to yield greater than a 50-percent chance of benefit or if the probability is less than 50/50. Dr. Merchant commented that such estimations depend on the individual trial and that a distinction needs to be made between saying the response is “not likely to change” and “we do not know if [a trial] will affect the intended change.” Dr. Mackall cautioned against providing a specific rate without data to support that number. Dr. Atkins stated that he considers an assessment of “not likely” to involve prospect of direct benefit to reflect a response rate of less than 5 percent and that such an assessment does not apply to a response rate described as or estimated to be less than 50 percent. He continued by noting that the probability for direct benefit and the language used depend on preliminary data and other studies conducted with the same or a similar approach. For example, if ten other trials using the same approach to replace a gene have an 80-percent benefit, then stating that prospect for direct benefit is “not likely” is the correct information to provide to the patient. In cases where data from preclinical models look promising but it is not known how the intervention will work in humans, the consent should state this clearly. In brief, and as discussed above, the language should reflect the available facts. The rates for recent studies, such as those reviewed by the RAC in 2014, should guide this discussion and future assessments.

Dr. Kodish pointed out that for most investigators, the consent document and communication during the consent process are not two distinct aspects of a clinical trial. Rather, investigators generally view the consent document as a template for conversations with the patient and, where applicable, family members. The information in the consent document is therefore important as a guide. Dr. Kodish stated, however, that additional training for investigators to learn how to properly consent subjects (as well as sufficient funding for such training) is warranted. He noted that, based on research involving pediatric oncology studies by his team and others, what is in the consent does not correlate well with what is being discussed, given the types of questions parents ask.

Dr. Roth-Cline commented on the strengths of ongoing multidisciplinary discussions which should help investigators better understand and more clearly convey various aspects of the research to participants. She cited the example of discussions between the clinical and pharmacology/toxicology teams as part of this process. She and Ms. Hardison noted further the challenge of being able to inform subjects clearly, given the differences in “language” and interpretations between the regulatory entities and patients. Dr. Hammarskjöld revisited prior discussions in which separate use of the words “experiment” and “therapy” is seen as problematic. She suggested using the term “experimental therapy” instead, because it reflects an intervention that is not generally approved and because most patients understand what the phrase means. Ms. Hardison agreed and considered use of “experimental research” or “experimental therapy” to be appropriate. Dr. Kohn noted that the dictionary definition of “therapy” indicates that the term implies an intervention that is not a guaranteed cure or that provides a clinical benefit but rather is given in an attempt to have a therapeutic response. Per this definition, “experimental therapy” may be somewhat redundant but appears acceptable.

Dr. Fost had similar concerns regarding the degree to which subjects actually comprehend what is in the consent document and the information reviewed during the consent process. He suggested that a future RAC meeting include a discussion about how to take advantage of the extensive body of research on ways to improve and assess comprehension and understanding as an essential component of consent. Dr. Kodish commented that while consumers and patients overall are increasingly more literate regarding health-related issues, there is still a long way to go to be able to effectively communicate what is involved in clinical studies, including the need for additional communications research.

Dr. Kohn presented some background information regarding the last question posed for discussion in this session, that is, whether patients should be informed about the risk of being excluded from future clinical trials, including gene transfer trials. To date, approximately 1,360 protocols have been submitted to OBA for RAC review. The inclusion and exclusion criteria of a small sample of these protocols, specifically, the last 20 protocols registered with OBA, were examined for language regarding prior participation in a gene transfer protocol. About half of the studies had an exclusion for participation in gene transfer trials that was not time-limited. One-third of this sample had a general exclusion for participation in a gene transfer trial, although one study allowed participation if the individual had previously been randomized to the placebo arm. About two-thirds of the sample had more limited exclusions, including participation in any protocol using genetically modified T cells or any gene transfer protocol with an integrating vector, exposure to any immunotherapy that targeted the same tumor antigen, use of any experimental cancer vaccine or tumor vaccine, and prior DNA immunotherapy.

Dr. Kohn noted that some patients in gene transfer protocols with an integrating vector have a suboptimal response and that the investigators have been discussing whether the protocol should be modified to offer a second round, which would involve bone marrow that has already been exposed to a retrovirus and adding a lentivirus. Dr. Kohn asked whether there is any specific policy to guide this discussion or whether cases in which a patient might be given a second integrating vector are considered on an individual basis. Dr. Bryan replied that FDA would review such scenarios on a case-by-case basis and ask the sponsor to provide the rationale for why it would be acceptable for the specific population in question to have an additional integrating vector. The overriding concern is that there could be delayed activity from the first product that would confound interpretation of data from the second product. Within the context of product development, the data collected for the second product could be valuable but would be difficult to assess. In general, however, caution should be taken when considering whether to include individuals who previously received gene therapy for a certain disorder. Dr. Nelson commented that one option, to provide an alternative to individuals who might not fit a protocol as designed for some of the reasons that Wilson mentioned, is expanded access. The standard there needs to be a reasonable possibility of direct benefit that's justified in the context of a life-threatening disease. If expanded access with a second intervention is under consideration, issues related to potential for direct benefit and modification of the IND should be fully explored, along with a compelling justification for the additional exposure. Dr. Atkins commented that while prior participation in a gene transfer protocol could compromise the interpretation of the study results, patient safety would not necessarily be compromised with a subsequent exposure. For example, an individual who was in an early gene transfer study or who received a product that was effective for their illness might be an acceptable candidate for another trial.

Situations where participation in a trial could preclude future options should be mentioned in the consent form.

Dr. Merchant asked Ms. Hardison to elaborate on her prior comments regarding how language means different things in different situations. Ms. Hardison explained that when people are in the hospital, they are thinking that the treatment or treatments that they receive are designed to have a clinical benefit. A lot of patients turn to academic medical centers expecting to be given innovative, experimental treatments, because they have not been helped in other settings. Thus, a large segment of the population appears to understand that experimental treatments exist. However, there is a presumption that the general public understands what constitutes clinical research, which is not the case for many patients. In addition, despite the best efforts by investigators to explain a study through direct discussion and the ICD, patients likely do not hear or understand that information because they are sick and in the hospital. One approach to address this issue is to better educate the public and patients on what is meant by clinical research so that there is a general, consistent understanding of the term.

B. Public Comment

Dr. Kohn read into the record a written letter from Dr. Robert Reinhard, addressed to Dr. Corrigan-Curay. The verbatim transcript of letter, as read during the meeting, is included as Appendix A.

X. RAC Bioethics Discussion Session III: Review of Selected Language from the NIH Informed Consent Guidance for Human Gene Transfer Trials

Lead Discussants: Rebecca Dresser, J.D., Washington University, St. Louis, MO
Laurie Zoloth, Ph.D., Northwestern University, Evanston, IL

A. Communication About Withdrawal from Gene Transfer Trials

Professor Dresser presented the background information and question posed for the first part of this session. Many gene transfer agents can persist for long periods or even indefinitely if the modified cells are stem cells. Research participants are told that they can withdraw at any time but cannot “undo” the gene transfer.

The following question was posed for discussion:

- What is the best way to communicate this to potential research participants?

The *NIH Guidance on Informed Consent for Human Gene Transfer Trials* states that participants have the right to withdraw from the study at any time, including during follow-up, and that the implications and consequences of withdrawal (from the intervention only or from the entire study) should be discussed as part of the consent process. The section on irreversible course of action in the NIH guidance elaborates:

“Participants should be informed that in the event that they withdraw, after receiving the experimental intervention, the intervention cannot be undone. If early withdrawal could pose any special risk of harm to participants or others, they should be described.”

Professor Dresser noted that one of the issues that has arisen consistently in the past year or 2 during RAC reviews is how to make sure that participants understand the points made regarding withdrawal from the study; that is, that withdrawing from a gene transfer trial does not mean that the agent administered as part of the study is or can or will be removed, but rather that the subject will no longer be monitored for health or research purposes once he or she leaves or completes the study. Sample consent language from the NIH guidance document to address these concerns includes the following:

“You do not have to be in this study. You can say no. If you join the study, you can leave it at any time. If you choose not to participate, there will be no penalties, and no bad effects on any benefits or medical care that you are entitled to get from this hospital or from your health care providers. If you leave the study, please tell the investigator or research coordinator. Then we will ask you to come back to the clinic for a final assessment and discussion of future treatment options.”

“Being in this study is completely voluntary. You may withdraw at any time without penalty, without loss of benefits to which you are entitled, and without affecting the medical care you get at our hospital. However, once you receive the gene transfer, there may be some effects that cannot be reversed.”

Professor Dresser found the NIH guidance to be helpful and considered the sample language to be appropriate as a starting point. The language should not automatically be used as boilerplate language for all protocols, however. Rather, the language should be assessed to determine if it is suitable for an individual study or if modifications are needed to address specific issues related to the protocol, intervention, or study cohort. Professor Dresser added that the larger problem in conveying this information to patients appears to be that it has not reached those involved in planning clinical research studies. Dr. Corrigan-Curay acknowledged additional sample language suggested by RAC members and asked whether the language currently included in the NIH guidance needs to be updated or revised in any way.

Dr. Atkins commented that these issues are not unique to gene therapy and that they also apply to situations such as when a patient is given an allogeneic bone marrow transplant or undergoes a liver or kidney transplant. In addition, it is not possible to know for every treatment how long the product or intervention will persist. Dr. Santana noted that, as with transplants, in certain oncology cases where the intervention cannot be removed or “undone,” patients are advised to continue to receive medical care and monitoring if they withdraw from a study, because of issues that could be identified that are relevant to their health. It would therefore be helpful to include a positive statement that although the subject is withdrawing, he or she should continue routine medical care for his or her condition and to talk to his or her physician about any side effects or any other issues and concerns. Dr. Kohn noted that the RAC usually makes this recommendation. The NIH informed consent guidance advises that investigators encourage (but not require) participants to return for follow-up in the event that they withdraw from the study if such follow-up is considered necessary or highly desirable for health and safety purposes. Dr. Nelson noted that FDA has guidance on not being able to withdraw data collected up to the time the subject leaves the study, which would undermine the integrity of the trial (“Data Retention when Subjects Withdraw from FDA-Regulated Clinical Trials,” released October 2008). With early withdrawal from a study, however, no additional data or samples would be collected.

B. Avoiding Therapeutic Misconception When Communicating About Long-Term Follow-Up and Reproductive Issues

Dr. Zoloth presented the background information and questions posed for the second part of this session. Gene transfer agents are unique in that long-term follow-up is often required because of the persistence of the agent can be years. Long-term follow-up may range up to 15 years. As in many other areas of investigational medicines, the effect of gene transfer agents on reproduction is not known. In trials involving individuals with terminal illness, where the likelihood of pregnancy is highly unlikely does the possibility of pregnancy need to be discussed and if so how can it be done in a sensitive manner that will not inadvertently foster therapeutic misconception?

The following questions were posed for discussion:

- In trials where the expected life expectancy may be less than a year, how can one communicate about long-term follow-up without leading to therapeutic misconception?
- In trials involving individuals with terminal illness, where the likelihood of pregnancy is highly unlikely, does the possibility of pregnancy need to be discussed? If so, how can it be done in a sensitive manner that will not inadvertently foster therapeutic misconception?

Dr. Zoloth noted that the consent language for explaining long-term follow-up for gene transfer trials is relatively straightforward. Two examples of sample language in the *NIH Guidance on Informed Consent for Human Gene Transfer Trials* follow:

“Long-term follow-up in gene transfer research allows for the collection of important information on the long-term safety and effects of the gene transfer intervention used in this study. The long-term follow-up planned for this study will occur [frequency] for [length of time]. It includes [study-specific information, as available; e.g., drawing a small amount of blood once a year; completing a health history questionnaire every year; having a biopsy of the injection site every five years; etc.]. The investigators will try to make it easier for you to participate in long-term follow-up by [study-specific information as available, e.g., using mail and telephone to collect some information; arranging with your local doctor to collect blood or biopsy specimens and send them to investigators; etc.]”

“At the end of the experimental phase of the study you will be asked to participate in the long-term follow-up phase for the rest of your life. Once a year, you will be asked to have your blood drawn (~[amount]) and answer questions about your general health and medical condition. The investigators may ask you to report any recent hospitalizations, new medications, or the development of conditions or illness that were not present when you enrolled in the study and may request that physical exams and/or laboratory tests be performed if necessary. We will also ask you to participate in the long-term follow-up phase if you leave the study early.”

Dr. Corrigan-Curay noted that the sample language describing long-term follow-up may be revised in response to recent recommendations.

Dr. Zoloth pointed to concerns regarding the requirement that the ICD for all gene transfer studies describe provisions for long-term follow-up. The inclusion of such information in consent documents for trials that enroll patients with perhaps a 3- month life expectancy is based on false assumptions. Further compounding this issue are statements about fertility and possible future pregnancies, which, along with long-term follow-up, are counterintuitive to discuss in such cases. The sample language in the *NIH Guidance on Informed Consent for Human Gene Transfer Trials* for reproductive risks is as follows:

“You should not become pregnant or father a child while taking part in this study. Women who are pregnant or breast-feeding may not be in this study.

“If you are a female who can have children, you will take a pregnancy test and the results will be given to you. You must confirm that you do not plan to become pregnant while on this study. If you are capable of giving birth or fathering a child, you must use an acceptable form of birth control.

“For women, contraception should go on for [period] after the last dose of the [gene transfer agent] to ensure that it has completely cleared from your body.

“For men, contraception should go on for [period] after the last dose of the [gene transfer agent] to make sure that all sperm in the body during the trial have been replaced. If you or your partner becomes pregnant, or you suspect that you or your partner is pregnant while in this study, notify the investigator at once.”

Dr. Zoloth recognized that the consent may need to discuss reproductive issues and long-term follow-up and that other consent and refusal language can be used for patients who have a disease that, for example, could be treated with less aggressive methods. However, she challenged the blanket inclusion of the above language in the ICD without consideration of the reality of the patients' status or situation. She noted that such language was included in some ICDs for protocols where participants had had their ovaries and uterus removed as part of an early intervention, and the gene therapy was being given to prevent metastatic disease. Dr. Santana commented that while some women in the latter (or a similar) example may not have had their reproductive organs removed, it is important to present information within the context of the disease and the protocol, with the driver in this case being the possibility of

reproductive potential. Regarding the importance of tailoring consent language to the study and the patient, Dr. Santana provided the example of men enrolled in a hemophilia trial who are capable of fathering a child and for whom reproductive issues may be of concern but who do not necessarily have a terminal illness or an incurable disease. Dr. Atkins noted how difficult and often dire these situations can be and noted that participants in Phase I trials do sometimes become pregnant. He commented that except for the rare situation where a study enrolls patients who have no uterus and no ovaries, the language about pregnancy prevention needs to be in the ICD.

Dr. Santana asked how the RAC addresses community standards for birth control. Dr. Kohn noted that the typical language states that the participant should be abstinent or use a barrier method or other effective contraception for a specified amount of time. He and others supported inclusion of “abstinence language” (e.g., “either/or”) to be responsive to certain religious groups and beliefs if pregnancy prevention is a condition of participation. Any requirements for male participants need to be stated, and all requirements should be included in the eligibility criteria. The pediatric perspective also needs to be taken into account, where applicable. Dr. Nelson noted that statements about use of acceptable forms of birth control are often interpreted to mean that some form of birth control is required even if one is not sexually active. For certain populations, the language can be softened to assure that it reflects the patients’ status.

In response to these concerns, the RAC concluded that the requirement for long-term follow-up of at least 15 years may be misleading for research participants with a disease with limited survival. It may be helpful to clarify with the regulatory authorities whether a 15-year follow-up period is actually required, as the most recent FDA guidance indicates that not all gene transfer products require such an extended follow-up. Any statement about long-term follow-up should be clarified to explain why this language is included and that it is not indicative of the investigators’ expectations regarding the potential efficacy of this approach. The RAC noted further that consent documents typically do not mention the fact that these research participants have very limited therapeutic options and a terminal disease, making the decision to enroll very altruistic. While these are sensitive issues to put in writing, additional language such as “There is no known or established treatment that can cure your disease” would communicate this clearly and balance other statements about a 15-year follow-up. Regarding information in the ICD for protecting against pregnancy, the RAC noted that when a treatment for a disease precludes pregnancy, such references seem unnecessary and may be upsetting to potential research participants. The NIH guidance may want to state that while an IRB may require certain standard language, investigators are urged to discuss this issue with the IRB within the context of the specific disease and population being studied. In response to this suggestion, Dr. Kohn pointed out that the RAC does not have control over local IRBs, which retain jurisdiction over their institution’s clinical trials, but the committee can make recommendations for consideration by the local boards. In addition, the FDA requirement for the 15-year follow-up is currently in place and will need to continue to be included in the consent document.

Dr. Zoloth noted the additional issues of independent versus private company-driven data and safety monitoring, publication review policies, and coverage of any injuries due to research participation, which were raised during a prior RAC ethics review. Industry reviews are when a company pays to monitor its own data and statistics as opposed to having an independent third-party review. The RAC discussion included whether the community should be moving toward a standard of independent review and oversight and whether having no or some limits on publication is acceptable. In addition, disclosure of any financial gain or conflicts of interest (COIs) will strengthen the consent process. The shift toward greater public oversight would help assure transparency of the entire clinical research process, including all study outcomes and analyses, and avoid publication bias. It was noted that these issues are usually handled at the contractual level between the sponsor and the study center or academic institution. In past cases, the RAC made removal of restrictions on publication a condition of approval. With the expectation that Phase I trials involve dose escalation until there is harm and that subjects may not be able to access health insurance for injuries experimental studies, the RAC developed language that companies should guarantee full insurance coverage for all side effects and injuries from the trial. Attendees recognized that the recommendations may be legally challenged. In addition, the RAC can make recommendations for uniform standards for all protocols, but it cannot enforce them because the committee is not a regulatory body. Dr. Corrigan-Curay conveyed NIH support for these principles but also recognized that there are and will be gaps for some studies and interventions. She noted the expansion in clinicaltrials.gov and the

recently published draft rule requiring all NIH studies to affirmatively post all their data in selected repositories and databases. There was general agreement that the RAC should make recommendations for independent data and safety monitoring, publication rights, coverage of any research-related injuries, and disclosure of any potential financial gain and COIs.

Drs. Corrigan-Curay and Kohn will compile the recommendations made during these sessions and will determine how best to convey any changes in the guidance to the community at large.

Dr. Atkins suggested putting together a list of criteria related to early-phase gene transfer trials that are distinct from the criteria of a standard Phase I trial and where more flexible consent language would be permissible.

C. Public Comment

No comments from the public were offered.

XI. Closing Remarks and Adjournment

Dr. Kohn thanked the RAC members and the OBA staff and adjourned the December 2014 RAC meeting at 4:47 p.m. on December 11, 2014.

(Note: Actions approved by the RAC are considered recommendations to the NIH Director; therefore, they are not considered final until approved by the NIH Director.)

Jacqueline Corrigan-Curay, J.D., M.D.
RAC Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and the following Attachments are accurate and complete.

This Minutes document will be considered formally by the RAC at a subsequent meeting; any corrections or notations will be incorporated into the Minutes after that meeting.

Date: _____

Donald B. Kohn, M.D.
Chair, Recombinant DNA Advisory Committee

**Attachment I:
Recombinant DNA Advisory Committee Roster**

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**Attachment II:
Public Attendees**

(This list includes only individuals who are not identified elsewhere in this document.)

Ben Berkman, National Human Genome Research Institute (NHGRI)
Linda Griffith, National Institute of Allergy and Infectious Diseases (NIAID)
Sara Hull, NHGRI
Carl June, M.D., University of California, San Francisco and University of Pennsylvania
John McNamara, NIAID
Gerald Shipley
Robert Witten, FDA

Attachment III: Abbreviations and Acronyms

AAV	adeno-associated virus
CAR	chimeric antigen receptor
CART-meso	chimeric antigen receptor T cell targeting mesothelin
CART19	anti-CD19 chimeric antigen receptor T cell
cDNA	complimentary DNA
COI	conflict of interest
CRS	cytokine release syndrome
CTX	cyclophosphamide
DLT	dose-limiting toxicity
DSMB	data and safety monitoring board
FDA	Food and Drug Administration
GeMCRIS	NIH Genetic Modification Clinical Research Information System
GMP	good manufacturing practice
GTSAB	Gene Transfer Safety Assessment Board
HAMA	human anti-mouse antibodies
HSCT	hematopoietic stem cell transplant
ICD	informed consent document
IL-2	human interleukin 2
IL2RG	human interleukin 2 gamma chain receptor
IND	investigational new drug
IRB	institutional review board
IV	intravenous
mAb	monoclonal antibodies
NCI	National Cancer Institute
<i>NEJM</i>	<i>New England Journal of Medicine</i>
NHGRI	National Human Genome Research Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NK	natural killer
NOAEL	no-observed-adverse-event level
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
PDA	pancreatic ductal adenocarcinoma
PI	principal investigator
QoL	quality of life
RAC	Recombinant DNA Advisory Committee
SAE	serious adverse event
scFv	single-chain variable fragment
SIN	self-inactivating
UPenn	University of Pennsylvania
VCN	vector copy number

Appendix A: Public Comments on Bioethics Discussion Session II

[This testimony is provided verbatim, as reported in the transcript of the December 2014 RAC meeting.]

Testimony of Robert Reinhard (via letter, read by Dr. Kohn)

Dear Dr. Corrigan-Curay:

Thank you for the opportunity to submit public comments for the RAC Bioethics Discussion. I direct my comments to Section II of the agenda. The agenda focuses on certain pediatric studies but may apply to many other studies. I previously offered comments on bioethics to the RAC for protocols on specific HIV gene therapy trials in September 13, 2013. Those trials were designed to explore potential for a cure, remission of HIV infection. They seek to eliminate the need for lifetime dependence on daily antiretroviral therapy, which is otherwise able to control infection in many circumstances, or they may provide a highly effective treatment even when conventional therapies have limited or no effect.

Building on my previous comments, please consider the following remarks. In HIV cure studies, desirable participants may include those whose infection is in early, primary, or acute stages ranging out to several years of chronic infection. Patients are often likely to include those whose infection is effectively controlled by current therapy suppressing viral replication without which viral rebound leading to a high morbidity and mortality results.

Indeed, it is the central mystery of viral persistence in the presence of effective therapy and rebound with therapy discontinuation which is the primary object of HIV cure research. These cohorts could be considered “healthy” under some criteria, but should nevertheless be considered candidates for study selection in early gene therapy trials, provided other cautions and risk avoidance protocols are in place.

Recent discussions of bioethics in HIV cure research emphasize the altruistic nature of ‘healthy’ participants in early trials as a primary fulcrum for permitting study risk so long as consent is meaningfully informational.

I request that the RAC engage in deeper bioethics discussion to expand the protections and other measures in trial design for these trials and not rely as heavily on pure altruism for justifying the study architecture. Altruism should not excuse avoiding risk reduction.

At least two trial design measures could be expanded towards this goal: (1) thoughtful use of ancillary care and (2) in the U.S., meaningful new provision of treatment for research-related injury. Tentative literature on providing ancillary care in clinical trials has emerged. Gene therapy trials for HIV infection when conventional therapy is the alternative are good candidates for this measure. This is true both for U.S. domestic research and for conducting these trials in other international settings.

I request the RAC work with others to develop appropriate ancillary care measures. Just for suggestions and nomination example, one could imagine offering, one, services to counter effects of HIV in aging and chronically infected individuals; or, two, pre-exposure prophylaxis therapy to committed partners of study participants during limited periods of drug therapy discontinuation. Other examples could be devised in a RAC consultation.

As to treatment for research-related injury, confusion remains regarding the effects of recent amendments under the Affordable Care Act specific to clinical trials. [Dr. Kohn stated here that the amendment is attached if anyone wants to read it.]

The amendment states that in government-funded trials for life-threatening illnesses, quote—and this is from the Act—“if a group health plan or health insurance issuer offering group or individual health insurance coverage provides coverage to a qualified individual, then such plan or issuer,” quote, “subject to Subsection C, may not deny or limit or impose additional conditions on the coverage of the routine patient costs for items and services furnished in connection with participation in the trial. Routine patient costs include all items and services consistent with the coverage provided in the plan or coverage that is typically covered for a qualified individual who is not enrolled in a clinical trial.”

And then the letter [from Mr. Reinhard] goes on to say, “Previously, informed consent most often told participants that the study sponsor would not cover research-related injury and that the injured parties should get treated under their insurance plans.” That is an empty instruction, since insurers typically excluded research-related injury from coverage. Under the Affordable Care Act amendment, substantial

and critical treatment services cannot be denied when injury occurs in many clinical trials. Informed consent should be revised to alert participants of these new rights.

Finally, the RAC agenda asks in addition, "As gene transfer agents may persist and have long-term effects, should research participants be advised that enrollment in one trial could preclude enrollment in other investigational studies?" The answer has to be yes, especially in these HIV exploratory studies. Participants need to weigh their options for eventually responding to effective cure and remission interventions.

Thank you for your consideration.

Sincerely,
Robert Reinhard