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Commentary

Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency

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ABSTRACT

It has been 9 years since Mr. Jesse Gelsinger died from complications of vector administration in a liver gene therapy trial of research subjects with a deficiency of ornithine transcarbamylase (OTCD). This study was performed at the Institute for Human Gene Therapy of the University of Pennsylvania (Penn) which I directed. His tragic death provoked a series of events that had implications beyond those directly involved in the clinical trial.

The events surrounding the death of this research subject have been the topic of much coverage and commentary in the popular press. The goal of this article is to share with you my reflections on the OTCD gene therapy trial and lessons that I have learned which may be of value to others engaged in various aspects of translational medicine.

The Phase I Gene Therapy Clinical Trial for OTCD

The gene encoding OTC is located on the X chromosome, meaning that males are more commonly affected with the disorder (reviewed in [1]). A complete absence of OTC function due to a severe mutation in its gene can have dramatic clinical consequences. Newborn males with a complete deficiency develop hyperammonemic coma following their first 3 days of life which, if untreated, is lethal. Even with current treatment, most survivors are left with severe cognitive deficits. Individuals who survive the newborn episode of coma can be partially treated with chronic drug therapy, although they are at risk for repeated episodes of protein-induced coma; the overall prognosis, despite excellent clinical care, is poor, and leads to the development of progressively worsening cognitive abilities and premature death in childhood. Females who carry one abnormal gene for OTC are usually without symptoms, although they can demonstrate protein intolerance especially at times of severe stress, such as following major trauma. Intermediate phenotypes are observed with males who have OTC mutations that render the enzyme partially defective.

The metabolic and clinical consequences of a deficiency of OTC can be corrected through liver transplantation, although there is significant morbidity and mortality from the procedure and the ongoing immune suppressive drugs [2]. Interestingly, the liver in patients with OTCD is generally normal except for the defect in this one gene. This suggests that an alternative approach to treating OTCD would be correction of the genetic defect or replacement with a normal version of the OTC gene in hepatocytes.

I was recruited to Penn in 1993 to establish the Institute for Human Gene Therapy. Soon after my arrival, I met with Dr. Mark Batshaw, who is a world expert in metabolic diseases with a particular interest in OTCD. Dr. Batshaw, together with his collaborators at Johns Hopkins University, developed the current pharmacologic therapy for OTCD [3]. We agreed that this disease would be an excellent initial model for testing liver-directed gene therapy and we initiated a collaboration to evaluate this possibility.

At the time of my recruitment to Penn, the field of gene therapy was still in its infancy. The first clinical trial of gene therapy for a genetic disease had been initiated, only 3 years prior to my recruitment, by Drs. Anderson and Blaese in research subjects with an inherited immune deficiency disease. Our studies would be the first to evaluate gene therapy directed to liver in humans with a genetic disease by direct administration of a vector. We were well equipped to develop the basic science and preclinical research to evaluate the feasibility of gene therapy for OTCD. The challenge, however, was to access the translational resources necessary to bring our basic research conducted in the laboratory into the clinic in the setting of first-in-human Phase I clinical trials. One approach to access these resources is through collaboration with the biopharmaceutical industry, which is more experienced than academia in issues related to translational and clinical research. This, however, was difficult to achieve in the early 1990s due to the nascent state of the field of gene therapy and the fact that OTCD was not a sufficiently large market to justify much commercial investment. Our approach, therefore, was to establish a translational capability internal to the academic program at Penn which would include production of clinical grade vector under good manufacturing practices, evaluation of the safety of the vector in animal models under good laboratory practices, design and conduct of the

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clinical trial under good clinical practices, and a quality assurance oversight group to assure compliance in all of these critical areas. This is, in fact, what we attempted to develop in the 1990s within the Institute for Human Gene Therapy. At the time the OTCD trial was put on hold in the Fall of 1999, the Institute for Human Gene Therapy was directly supporting Investigational New Drug protocols (INDs) for seven clinical trials spanning a wide range of diseases.

The key step in advancing gene therapy for OTCD was to develop a gene delivery vehicle capable of shuttling a normal version of the OTC gene into hepatocytes. This was accomplished through the use of an attenuated or disabled version of an adenovirus which had been engineered to express the normal OTC gene. Dr. Batshaw and I were able to demonstrate some level of efficacy using an adenoviral vector in a mouse model of OTCD [4,5]. Based on these preliminary data, we assembled a team of investigators to further this program and submitted a Program Project Grant to the NIH to support the work. Responsibilities were distributed amongst three scientists with complementary backgrounds in order to access the scientific and clinical experiences necessary to: (1) perform the preclinical studies, (2) to conduct the clinical trial, and (3) to manage financial and non-financial conflicts of interest of the investigators. A more thorough discussion of these conflicts of interest is provided in later sections of this commentary. I provided expertise in vectors and preclinical gene therapy and served as sponsor of the IND application to the FDA and was co-Principal Investigator on the grant. Dr. Mark Batshaw is an expert in OTCD and a practicing pediatrician. He served as Principal Investigator on the Institutional Review Board (IRB) submission to the affiliated pediatric hospital, The Children's Hospital of Philadelphia, and was the Principal Investigator on the grant to the NIH. We recruited the help of a colleague of ours, Dr. Steve Raper, who is a general surgeon and had experience in clinical gene therapy for treating liver disease using an alternative approach based on transplantation of genetically modified cells. Dr. Raper was the Principal Investigator of the protocol submitted to the IRB at the Hospital of the University of Pennsylvania where the subjects were admitted; in this capacity, he served as the physician of record for these individuals while in the hospital. He was also co-Principal Investigator on the grant.

The grant was submitted on March 23, 1994 and we soon developed promising preclinical data that led to the submission of an IND to the FDA approximately 2 years later. The preclinical data developed to support this IND application involved efficacy experiments in the mouse model of OTCD and safety assessment studies performed both in mice and in various types of non-human primates. Using the first generation of the adenoviral vector (i.e., deleted of the E1 gene), we showed a nearly complete correction of the metabolic defect in the mouse model for OTCD that lasted for several weeks to 1 month [4,5]. High doses of the first-generation vector were administered to mice and rhesus macaques in order to assess potential toxicities [6,7]. The primary toxicity we observed was related to the development of self-limited hepatitis approximately 1 week after vector administration. At the highest dose of the first-generation vector, monkeys developed a syndrome of severe liver damage and a clotting disorder that led to death or required euthanasia within several days [6]. Between the time of the initial IND submission on April 18, 1996 and when we received permission to enroll subjects on October 21, 1996, we brought forward at least two improved versions of the OTC adenoviral vector called second- and third-generation vectors. The trial proceeded with the third-generation vector which showed in mice a substantially improved toxicity profile over what was obtained with the first-generation vector [8]. In an attempt to assure safety in the clinical trial, we proposed to administer third-generation vector at a maximum dose that was 17-fold lower than the dose of first-generation vector that showed severe toxicity in macaques. We felt that this would provide us with a 100- to 1000-fold margin of safety in terms of vector dose. Based on discussions with FDA, we designed a final study to simulate the clinical trial in which third-generation vector was administered to baboons at the starting and ending doses proposed for the clinical trial. Only minor and transient laboratory abnormalities were observed in the high dose baboon group [9].

The team engaged in an extensive set of discussions regarding the structure of the clinical trial [10]. Various aspects of the study design were quite standard such as the fact that it would be a Phase I dose escalation study using safety measures as the primary endpoints, although metabolic correction was also considered. We selected six groups of subjects, with three subjects per group, beginning with a very low dose vector, and escalating half-logs between cohorts to a maximum dose of vector as described above.

One controversial aspect of the trial related to the eligibility criteria for participation which was restricted to adults. Consideration was also given to enrolling newborns in the setting of, or immediately following, resolution of the neonatal hyperammonemic crisis. This was rejected based on concerns over informed consent which would have to be provided by a guardian and the "coercive" nature of the situation in which the guardian would need to provide this consent (i.e., at a time when the child is severely sick and at high risk of dying and/or becoming mentally retarded). The decision to proceed with adults followed extensive discussion with scientists, metabolic disease physicians, bioethicists, and representatives of the Urea Cycle Foundation. Our decision to focus on adults was fully endorsed at the time the protocol was initially reviewed by the relevant regulatory agencies and oversight committees. This decision was questioned after the trial was stopped because we had subjected volunteers with little to no disease-associated morbidity to vector-associated risks that were essentially unknown in humans. In fact, the bioethics community has debated the appropriateness of clinical trials in healthy volunteers in which participation is associated with more than minimal risk [11]. For example, the first evaluation of toxicity for many novel cancer treatments and some applications of gene therapy are performed in subjects more severely affected by their disease. In retrospect, I have questioned the wisdom of this decision, although beginning the study in younger, more severely affected individuals presents a different set of ethical dilemmas.

The first subject was dosed with vector on April 7, 1997. The clinical trial progressed through the first five cohorts without serious adverse events, although toxicity was indeed observed as described [10]. These toxicities included self-limited fever and flu-like symptoms and several transient laboratory abnormalities (e.g., transaminitis, hypophosphatemia, and thrombocytopenia). The first subject of the sixth cohort (i.e., OTC018) received the highest dose of third-generation vector which was 17-fold lower than the dose of the more immunogenic first-generation vector that caused severe toxicities in non-human primates. This 19-year-old female experienced the same toxicity seen in previous human cohorts that included fever and flu-like symptoms with some transient laboratory abnormalities. The second subject in this cohort was an 18-year-old male, Mr. Jesse Gelsinger[1] (OTC019). He received vector on September 13, 1999 and experienced a dramatically different response that ultimately led to systemic inflammation and multi-organ failure; this fulminate acute inflammatory response to vector was different from the toxicities observed in the other human research subjects and in the preclinical studies [12]. Despite attempts of the clinical team and all available consultants to support Mr. Gelsinger through this severe inflammatory episode, he died

[1] The name of this research subject was disclosed extensively in the popular press with the apparent consent of his family. We therefore will refer to him as Mr. Gelsinger throughout the manuscript.

98 h after receiving vector. The trial was put on clinical hold at this time and eventually withdrawn without accruing additional research subjects. Almost 2.5 years transpired between dosing of the first and last research subjects which was due to the conservative dosing schedule in the protocol that allowed for safety assessment between subjects within a cohort and between cohorts, as well as the challenge of finding volunteers with this rare disease who were willing to participate and who fulfilled the restricted eligibility criteria.

In order to identify the mechanism(s) of this severe toxicity observed in Mr. Gelsinger, we initiated a series of studies that continue to this day. Permission to conduct an autopsy was granted from the Gelsinger family and biological samples were further analyzed suggesting vector-induced activation of innate immunity, leading to an acute release of inflammatory mediators [12]. Additional animal experiments were conducted focusing on components of the vector preparations that may activate innate immunity. Problems with the actual preparation of vector administered to Mr. Gelsinger such as contamination were ruled out. Our current hypothesis is that certain protein components of the vector capsid, which are necessary for the vector to function, inadvertently trigger antigen presenting cells to elaborate inflammatory cytokines [13,14]. Unfortunately, modifications of the vector genome will not and apparently did not circumvent these innate immune responses.

What remains unclear is why the response to vector in Mr. Gelsinger (i.e., subject 019) was so exaggerated as compared to what was observed in the other subjects, including subject 018, who received the same dose of vector. Several mechanisms are being considered, such as (1) a genetic predisposition to enhanced innate immunity or (2) immune memory to the vector and/or previous exposure to adenoviruses in the setting of natural infections that enhances the response of the host to a second exposure to the virus/vector. It is interesting that the level of pre-existing immunity to the vector as measured by neutralizing antibody was higher in Mr. Gelsinger (titer of neutralizing antibody (NAB) of 1/80) than in subject 018 (titer of NAB at limit of detection which is 1/20). Recent studies in mice and NHP, however, have not been able to demonstrate such a dramatic difference in toxicity as a function of pre-existing immunity to vector [15,16].

Consequences of the OTCD Trial

When it became clear that Mr. Gelsinger was suffering from a severe reaction to the vector, the team informed his family and notified all relevant national and local agencies including the IRBs, the Recombinant DNA Advisory Committee (RAC) of the NIH, and the FDA.

Subsequent inquiries from the press and congressional investigations about adverse events in other gene therapy trials determined that there was confusion as to the need for reporting adverse events to the RAC. Although the toxicity seen in Mr. Gelsinger was reported promptly, it appeared there was under-reporting of adverse events in many gene therapy trials, which fueled concern over the federal oversight of gene therapy.

Both Penn and the Children's National Medical Center, where Dr. Batshaw was located at the time, initiated internal investigations about the conduct of the OTCD trial. The Washington Post published a series of investigative reports alleging non-compliance in several aspects of the trial management. Parallel investigations by multiple federal regulatory agencies were initiated including the Office for Human Research Protections, the NIH, the FDA (including separate audits of the clinical trial, the safety assessment studies, and the vector manufacturing), Committees from both the United States Senate and House of Representatives, and the United States Attorney for the Eastern District of Pennsylvania. These investigations resulted in a number of allegations of non-compliance in the formal evaluation of safety in preclinical models and in the conduct of the clinical trial. Questions were raised about non-compliance in a number of areas including: documentation of findings, timeliness and accuracy of reports to the IRB and FDA including summaries of adverse events, completeness of protocol mandated tests, adherence to eligibility criteria and stopping criteria, adequacy of training of clinical staff, delivery and content of the consent process, completeness of monitoring of subjects following vector dosing, and timely notification to FDA of animal toxicity data acquired subsequent to initiation of the study. The investigations ultimately led to a settlement with the government without admission of wrongdoing by the institutions or the individuals including Drs. Batshaw, Raper and myself.

Responding to the multiple investigations provided Drs. Raper, Batshaw and me an opportunity to review all aspects of the events that led up to the trial, as well as its conduct. It became apparent there were shortcomings in several key aspects of the trial; a number of the allegations asserted by the government indeed had merit. This level of non-compliance is inexcusable and as sponsor of the IND and Director of the Institute for Human Gene Therapy at that time, I accept full responsibility for these problems. I truly believe, however, that the team of physicians, scientists, nurses, and administrative staff that were charged with conducting the clinical trials were an extremely committed and dedicated group of individuals who did the best with what they were provided, and never intended to misrepresent or withhold information.

The events surrounding the OTCD trial occurred at a time when there was an emerging concern at a national level about the existing infrastructure to oversee clinical research. Around this time, all clinical research was temporarily shut down at several institutions, including University of Oklahoma and Duke University, due to concerns over the institution's oversight of human subject research. The Secretary of the Department of Health and Human Services at the time, Dr. Donna Shalala, in an article published in the *New England Journal of Medicine*, pointed out the importance of bolstering this critical infrastructure, citing the OTCD trial as an example of why this was necessary [17].

In fact, there have been substantial reforms across many institutions in the U.S. in terms of oversight of human subject research. This transformation at Penn has been dramatic. We have evolved from 1999, where we had four IRBs with a staff of five, to 2008, where we have revitalized IRBs that number eight with a current staff of 23, improved institutional SOPs, mandatory training and education, an Office of Human Research with a staff of 14, a Faculty Advisory Committee charged with monitoring and oversight, and a Clinical Research Advisory Committee. We have also received accreditation by the AAHRPP, a national non-profit agency established to accredit human research protection programs. The kind of training, support, and oversight currently provided to academic investigators involved in clinical trials at many institutions will go a long way in avoiding the kind of problems encountered in the OTCD trial. I say this not to deflect blame, but to highlight some of the positive consequences that have emerged following Mr. Gelsinger's tragic death.

The purpose of this commentary is not to respond to each of the allegations that emerged from the investigations, but rather to learn from my experience as an investigator in the OTCD gene therapy trial.

Several lessons that I have learned from this experience are presented below.

Lesson #1: The clinical protocol is a contract with the research subjects and regulatory agencies that must be strictly and literally adhered to. A major challenge was the fact that a clinical trial of this complexity using gene transfer technology not previously tested in humans had never been conducted in an academic set-

ting, and its implementation was complicated by a variety of factors. Examples of problems with the clinical protocol and its implementation are provided below.

The protocol was designed to allow for evaluation of the consequences of gene transfer for a period of time after dosing before the next subject within a cohort could be dosed; a formal review of the cumulated data was conducted and submitted to FDA between cohorts before we were allowed to proceed to the next dose. These summary data were used to determine whether to continue dosing and, if so, whether the data would compel us to revise the protocol. An example was the observation of transient thrombocytopenia in an early cohort, which led to the inclusion of measures of disseminated intravascular coagulation (DIC) in all subsequent subjects. The ongoing evaluation and reporting of data during the trial resulted in a very active and productive dialog with FDA that included a total of 151 communications, 86 of which occurred before the trial was put on hold relating to the first 17 of 18 total research subjects. The extensive ongoing data analysis and communications with FDA contributed to the long duration of this trial which took almost 2.5 years to dose 18 volunteers.

The actual protocol became a living document with changes occurring in real time. The team attempted to capture these changes through four different protocol revisions, with up to 54 changes included in some of the revised protocols. The investigations revealed, however, that we did not adequately document and report all of the protocol modifications to the IRBs and to the FDA. This led to confusion amongst members of the team and misunderstandings between the FDA and the team.

Another problem that became evident during the investigation is that aspects of the protocols did not provide sufficient clarity regarding key issues such as eligibility criteria. This led to the allegation that Mr. Gelsinger was not eligible for participation in the trial based on several issues including a measurement of serum ammonia that was greater than the acceptable level of <70 μM. In fact, this threshold had been increased from 50 to 70 μM in an earlier revision to the protocol. In establishing this criterion, the clinical investigators did not take into account the substantial fluctuation in plasma ammonia that characterizes this disorder, nor did they specify the specific time(s) it was necessary for the serum ammonia to be below this threshold level. Multiple serum ammonia measurements were obtained prior to and immediately after dosing Mr. Gelsinger, which fluctuated around the threshold of 70 μM. The clinicians felt this kind of fluctuation was not clinically relevant and therefore enrolled Mr. Gelsinger. However, the protocol was not written to include clinical relevance of metabolic measures in assessing inclusion criteria providing credence to the FDA's concerns.

It is absolutely critical that the investigator view the protocol as a document that must be strictly adhered to. These documents need to be clearly written and any changes clearly highlighted and shared with all relevant agencies prior to incorporating the changes into the conduct of the trial.

A key question is how these problems could have occurred? The fact is that much of the study was done according to protocol in a fully compliant way. It is clear now that the Clinical and Quality Assurance (QA) groups did not have the resources necessary to assure *complete* compliance for such a dynamic and complex protocol. They were asked to cover too much territory; each clinical research nurse oversaw as many as three gene therapy protocols at any one time, while the QA group, which numbered seven staff members at its peak, was responsible for most aspects of GMP, GCP, and GLP compliance for up to seven active INDs. Support for these programs was provided primarily from grants and contracts that, individually, did not provide sufficient Clinical and QA resources to fully support specific protocols. However, it was my responsibility to secure the necessary resources to conduct each study in a fully compliant way and we should not have proceeded if the resources were insufficient.

Lesson #2: If you think about reporting – then do so! An example of this is related to the allegation that we had not reported deaths of monkeys in a timely manner. As noted earlier, we had performed a series of studies in rhesus macaques with first-generation adenoviral vectors in which the animals did die and suffered from hemorrhagic bleeding disorders at very high doses [6]. Subsequently, in the context of a separate and unrelated liver cancer gene therapy trial, additional experiments were performed with adenoviral vectors in rhesus macaques. Animals that received first- and second-generation vectors suffered fatal consequences at the highest vector dose similar to the studies performed with first-generation vector in preparation for the OTCD IND that were reported to the RAC, IRB, and FDA. The new information from the more recent experiments related to studies with the third-generation vector of the type used in the OTCD trial administered at the dose that caused lethal toxicity with the first- and second- generation vectors; these animals did in fact survive, although they did have cutaneous manifestations of low platelets called petechiae and transient laboratory abnormalities. The OTCD team did discuss the implications of the additional primate data on the ongoing OTCD study and concluded that these additional studies did not provide additional new information beyond what was initially submitted to the RAC and FDA and did not require immediate reporting in the context of the OTCD study. The QA group recommended inclusion of the data developed for the cancer trial in a subsequent annual report to the FDA regarding the OTCD trial which at the time the trial was put on hold had not yet happened. Our conclusion regarding the new monkey data and its relevance to the ongoing OTCD trial and the plan for reporting, which was documented in team meeting minutes, was deemed by FDA to be incorrect based on the agency's review of this information first provided to them immediately after the trial was put on hold. I conclude that any preclinical or clinical data that could conceivably have an impact on an ongoing trial should be reported promptly to both the FDA and the IRB as well as potential research participants. If you think about reporting it, then do so!

My retrospective analysis of the way this issue was handled raised a potential problem with the dynamics of the research group. As described above, responsibilities for the protocol were distributed amongst three physician-scientists with complementary skills and experiences. Decisions were made in the context of "team meetings" with all constituencies present. This approach provided transparency for key decisions and invited input from all members of the group to better inform these decisions. A potential disadvantage of this approach is that it diverts responsibilities from individuals to the team, creating the sense of diminished individual accountability, which was not its intent and may have played a role in some of the decisions made during the conduct of the trial such as the one related to timing of disclosure of these additional animal studies. The fact is that this decision was ultimately mine as sponsor of the IND, irrespective of what others thought, and that I have to take sole ownership of the decision.

Lesson #3: It is very difficult to manage real or perceived financial conflicts of interest in clinical trials. One of the most troubling allegations that surfaced following the OTCD gene therapy trial was that decisions were influenced by the potential for personal financial gain, especially as it related to my affiliation with a gene therapy biotechnology company called Genovo, Inc. These allegations emerged at a time when more global concerns had been rising regarding financial conflicts of interest in other clinical trials conducted in the United States. Evaluation of this issue often attempts to differentiate real conflicts of interest due to possible financial gain from situations where there is no potential for financial gain but that there is the perception that this may occur (i.e., perception

of conflict of interest). As I will argue below, this distinction is irrelevant when considering management strategies and consequences of conflicts of interest in clinical trials. Reference to "conflicts of interest" will encompass both real and perceived conflicts.

My analysis of this issue focuses on financial conflicts of interest of the investigator and does not address the even more complicated issue regarding financial conflicts of interest of the institution where the research is performed. The institution may benefit directly from the success of companies to which it has licensed technology and may benefit indirectly from research conducted by its faculty in terms of increased numbers of grants and donations.

My immediate response to the allegation that I had a financial conflict of interest was that it was unfounded, based on several considerations. The concept of the OTCD gene therapy program and the preparation of the grant which included the clinical trial occurred before Genovo received funding and established programs. Genovo was not the sponsor of the clinical trial, provided no direct support for the conduct of the trial, and there appeared to be little commercial interest in the disease since it was so rare.

Upon reflection, I realize my initial reaction to these allegations oversimplified what is a more complex issue and that concerns raised about the potential for financial conflicts of interest in my role as sponsor of the IND were indeed legitimate. The fact is that I was a founder in a biotechnology company focused on gene therapy while being directly involved in gene therapy clinical trials as a sponsor of the respective INDs. The juxtaposition of these two facts, independent of their connection, raised the perception of a potential financial conflict; in this kind of situation, perception can quickly become reality. Furthermore, it is virtually impossible to convincingly rule out the absence of bias in one's decisions due to financial or non-financial conflicts of interest; one cannot prove a negative and any attempt to do so sounds defensive and lacks credibility. Finally, both Penn and I owned stock in Genovo and it is possible that a success in the OTCD gene therapy trial could enhance the value of Genovo (and other gene therapy companies) through encouraging proof-of-concept clinical results. For example, any clinical success would likely bolster investor support for the commercial development of gene therapy that could enhance the value of most existing gene therapy companies including Genovo even if they were competitors of Genovo.

In further evaluating the role this conflict may have played in the conduct of the OTCD trial, I have reflected on the professional motivations of academic scientists such as myself and how these factors may influence decisions of the kind that have been questioned during the investigations. My primary motivation in pursuing the OTCD trial was to help children with lethal inherited diseases. If our study was successful, the same approach could potentially be applied broadly across a wide array of rare disorders. It should be recognized, however, that academic medicine is a competitive profession with the primary measure of success being recognition by your colleagues of your research accomplishments. This recognition is critical to sustaining one's research agenda through the successful competition for grants and the awarding of academic promotions and tenure. The quest for this recognition influences work plans, priorities and decisions, and is a requisite means to the ultimate goal of furthering science. Incorporating the incentive for personal financial gain into this complex dynamic is problematic specifically as it relates to the conduct of clinical trials. I learned it is very hard to convincingly uncouple drivers for academic success from the incentives derived from potential financial gain. My conclusion is that the influence of financial conflicts of interest on the conduct of clinical research can be insidious and very difficult to rule out, as I have decided was the case in the OTCD trial.

Genovo was founded before I moved to Penn as a virtual company that had acquired some of my intellectual property from the University of Michigan. Soon after my arrival to Penn, Genovo was provided the opportunity to secure substantial financial investment with a significant portion coming to my laboratory as sponsored research. Continuation of my relationship with Genovo required review and approval by Penn which undertook a thoughtful and diligent analysis of the potential conflicts of interest and put in place management plans including multiple restrictions on my activities, oversight specifically designed to manage my relationship with Genovo in the form of two committees, and a written disclosure to any subject enrolled in an Institute for Human Gene Therapy clinical trial describing a potential financial conflict of interest that Penn and I had.[2] The restrictions, aggressive in comparison to standards of the time but more standard now, included, but were not limited to: (1) waiving my rights to royalty proceeds from commercial products developed and sold by Genovo that I otherwise would have been entitled to per the inventor's distribution policy of Penn, (2) no formal employment position with Genovo and no membership on Genovo's Scientific Advisory Board, and (3) stock that was limited to less than 30% and was non-voting. The fact is that these management tools proved inadequate to assuage the concerns of financial conflicts of interest influencing my behavior in the context of the OTCD trial when reviewed following the death of Mr. Gelsinger. I conclude that it is impossible to manage perceptions of conflicts of interest in the context of highly scrutinized clinical trials, particularly where there is a tragic outcome. Disclosure of the conflict is not enough as has been suggested by others; some have suggested disclosure may actually exacerbate bias [18]. Allegations of this nature in the setting of clinical trials can erode the public's confidence in biomedical research and have far reaching negative effects and should be avoided.

My suggestion is to take a conservative approach in addressing real or perceived financial conflicts of interest in clinical trials until the community of stakeholders establishes clear and generally accepted guidelines. This conservative approach would limit direct participation in clinical trials, as defined by those responsible for the actual conduct and audit of the trial, to individuals that have no real or perceived financial conflicts of interest. This policy would not rule out participation of individuals with conflicts of interest in the preclinical work and design of the clinical trial and interpretation of clinical data; this is important since individuals with potential financial conflicts of interest may be the ones with the most knowledge of the science and the most experienced with the patient populations who are under study. However, the ultimate authority and responsibility for all aspects of the clinical trial should reside with those directly affiliated with the trial and without financial conflicts.

It must be realized, however, that a zero tolerance for real or perceived financial conflicts of interest in clinical trials (i.e., preclude the direct involvement in the clinical trial of anyone with a real or perceived financial conflict of interest) can limit the contribution of the physician-scientist to the process of bench-to-bedside or what we now call translational research. Under a zero tolerance policy, any scientist that contributes to a basic discovery that leads to a licensed patent would be precluded from direct participation in clinical trials that utilize the associated technology, independent of whether s/he has an affiliation with a company. The investigator would receive a portion of any revenue provided

[2] On page 11 of the OTCD gene therapy trial consent document under the header of "Sponsor Information" just above the signature space, the following statement was included: "Please be aware that the University of Pennsylvania, Dr. James M. Wilson (the Director of the Institute for Human Gene Therapy), and Genovo, Inc. (a gene therapy company in which Dr. Wilson holds an interest) have a financial interest in a successful outcome from the research involved in this study.

from the licensee to the institution as part of the license which is standard practice in most institutions. Such restrictions could have the unintended consequence of impeding scientific progress. Balancing and formulation of these rules is extremely challenging but needs to be addressed.

Lesson #4: Informed consent may require objective third party participation. The OTCD gene therapy protocol and the associated consent document underwent extensive review including IRBs at three institutions, the Recombinant DNA Advisory Committee, the Oversight Committee of the General Clinical Research Center of the University of Pennsylvania, and the FDA. The subsequent investigations criticized the original consent documents for not adequately articulating the risks and for not disclosing the fact that monkeys died after being administered high dose vector. In formulating the original consent documents, the team incorporated input from the multiple constituencies noted above. Concerns were also raised that consent documents were not adequately revised during the study to incorporate disclosure of the toxicities, particularly while verbal references were made regarding encouraging results in previous subjects. Clearly, we could have done a better job in these important areas.

Adequately informing the subjects about the risks and benefits of the trial was indeed a challenge due to the complex nature of the study and the fact that this was one of the first applications of *in vivo* gene transfer in subjects with a genetic disease. This is further complicated by the requirement to prepare the consent document in a way that would be understandable to the subject; however, there are no explicit guidelines from FDA or OHRP indicating an appropriate age or grade level for readability/comprehension. Rather, the current guidance from OHRP focuses on informed consent as a process (http://www.hhs.gov/ohrp/informconsfaq.html). Many IRBs have adopted a 6th – 8th grade readability threshold for informed consent documents based on literacy rates and other factors [19]. An example of this challenge relates to a summary of the animal studies that included multiple strains of mice and two types of monkeys (macaques and baboons) injected via different routes with three different generations of vectors.

Consent was divided into two stages: the initial evaluation which was done when the subject was an outpatient, weeks to months ahead of the trial, and at the time of vector infusion, which occurred during the subject's admission to the hospital. The clinical team headed by Steve Raper took the lead in explaining the protocol and obtaining consent.

The intense scrutiny this issue received following Mr. Gelsinger's death served to illustrate some of the challenges we face in translating cutting edge discoveries into clinical evaluation, especially as it relates to informed consent. My reflections have focused on two areas. The first of which relates to non-financial conflicts of interest when the individuals involved in informed consent are also scientists behind the research or clinicians involved in the care of the patient. The scientists behind the technology believe in the potential of the technology and pursue its development with zeal in order to overcome significant uncertainties and road blocks that inevitably come up in the laboratory. This "belief" in the technology may make it difficult to objectively represent its potential limitations to the research subject in the context of informed consent. Concerns have also been raised when the Principal Investigator of the trial (i.e., the individual responsible for the well-being and consenting of the research subject) is also a physician who has or may provide medical care for the subject/patient. This dual role/relationship may confuse research with clinical care and puts the investigator in a position to heavily influence the patient's/subject's decisions.

We tried to manage these issues by precluding me from interacting with the subjects or participating in their management based on the concern that I discovered some of the technology and therefore was invested in its success. We decided to recuse Mark Batshaw from the actual consent process since he is a metabolic disease clinician who was or may become a physician for the subjects/patients. Steve Raper was viewed as the most objective in serving in the role as clinical Principal Investigator and had the requisite qualifications based on his previous experience in clinical gene therapy and his clinical practice as a general surgeon who does procedures involving the liver.

The challenge is that the most qualified individuals to participate directly in the clinical trial are those who developed the technology and those with knowledge of the disease which unfortunately are also those with potential non-financial conflicts of interest. The crux of the problem is to assure that the subject receives a balanced and unbiased view of the risks and benefits of his/her participation in the trial and that s/he can make decisions without influence or concern over negative consequences.

One approach that has been proposed to address these non-financial conflicts of interest is to involve a third party "patient advocate" in the consent process. While this may not be feasible or even necessary in all clinical trials, it would seem prudent to consider in some cases, such as relatively novel and untested technologies in sick research subjects and/or rare diseases. An example of the apparent successful use of a patient advocate has been in the evaluation and use of the implantable artificial heart [20].

My second concern relates to the assessment of risk for a new technology that has not been tested in humans, such as was the case of adenovirus vectors for liver-directed gene therapy of subjects with a genetic disease. The onus is on the scientific team to develop as much preclinical data as they can to assess the potential utility of the technology and the types of toxicity that may be seen in humans. The fact is, however, that one must concede some level of uncertainty regarding the relevance of the preclinical models until they can be reconciled with human data. This uncertainty must be reflected clearly in the consent process.

In summary, I have highlighted some of the key lessons I learned from the OTCD investigations. This event had far reaching effects on the trajectory of gene therapy research and oversight of all clinical trials. My deepest regret is that a courageous young man who agreed to participate in this clinical trial with the hope of making life better for others with this disease lost his life in the process. The immunologic response that precipitated the lethal syndrome of systemic inflammation was unanticipated and not predicted based on the preclinical and clinical data available at the time. However, some of the problems in the design and conduct of the clinical trial that surfaced in the subsequent investigations were real and absolutely unacceptable and ultimately were my responsibility. The fact is that Mr. Gelsinger and his family, and all individuals who so selflessly volunteer to participate in clinical trials, deserve better. They deserve a clear explanation of the risks and benefits of the clinical experiment that is objective and not influenced by the biases of the professional and clinical interests of the participating investigators. They deserve a clinical trial that is conducted in strict compliance with all regulations and not tainted by the perception of financial gain by individuals and institutions. And finally, they deserve our commitment to address these complex problems so that the promise of new therapeutic strategies can realize their potential in treating their diseases.

Acknowledgments/Conflict of Interest Disclosure

The concept of writing this article emerged during discussions with the government regarding a settlement agreement. The goal was for me to openly discuss the lessons I learned from this experience to educate other investigators and minimize similar problems

in the future. All investigations and litigation about this case have been completed and resolved. Furthermore, there are no agreements that restrict me in expressing my views openly on this topic. My thanks to the many colleagues who reviewed earlier drafts of this manuscript and provided excellent and often poignant feedback.

I am an inventor on gene therapy patents that have been licensed to multiple biopharmaceutical companies and in the past five years had served as a consultant and received grants from various companies.

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