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The Death of Jesse Gelsinger: New Evidence of the Influence of Money and Prestige in Human Research

Professor Robin Fretwell Wilson†

I. INTRODUCTION

Ten years ago, Jesse Gelsinger died while participating in a human gene-therapy trial at the University of Pennsylvania ("Penn"). His death came to signify the corrosive influence of financial interests in human subjects research. After Jesse's death, the media reported that one researcher, Dr.

† Class of 1958 Law Alumni Professor of Law, Washington and Lee University School of Law. This Essay draws on Robin Fretwell Wilson, Estate of Gelsinger v. Trustees of University of Pennsylvania: Money, Prestige, and Conflicts of Interest in Human Subjects Research, in HEALTH LAW AND BIOETHICS: CASES IN CONTEXT 229 (Sandra H. Johnson, Joan H. Krause, Richard S. Saver, & Robin Fretwell Wilson, eds., 2009). I am grateful for feedback I have received during presentations at The University of Illinois College of Law, Wake Forest University School of Medicine, Drexel University School of Law, Saint Louis University Center for Health Law Studies' Distinguished Speakers Series, Carilion Medical Center, the 35th Annual Conference of the Public Responsibility in Medicine and Research (PRIM&R), and at Boston University's symposium "Follow the Money: The Impact of Economic on the Delivery of Health Care." I am indebted to Bob Brummel, Charles Hite, former Assistant U.S. Attorney David Hoffman, David Hyman, Fran Miller, Alan Milstein, and especially to Paul Gelsinger for their insight and assistance with this Essay. This is for Fran Miller, who has always inspired me.

† See, e.g., Patricia C. Kuszler, Biotechnology Entrepreneurship and Ethics: Principles, Paradigms, and Products, 25 Med. & L. 491, 495 (2006) ("[L]apses in human subjects protection remains an ever-present hazard. This has been exemplified by a series of high profile research ethics scandals in the U.S.—the Jesse Gelsinger case in which a research subject in a gene-therapy experiment died and it was alleged that the researchers' financial interest in the vector influenced them to prematurely engage in the clinical trial that resulted in Mr. Gelsinger's death."); Trudo Lemmens, Leopards in the Temple: Restoring Scientific Integrity to the Commercialized Research Scene, 32 J.L. Med. & Ethics 641, 645 (2004) ("[F]inancial interests may negatively impact researchers' dealings with research subjects during a trial. When huge profits lure, and pressure mounts to bring novel drugs or therapies quickly to the market, potential risks may be perceived somewhat more lightly, and inclusion
James Wilson, held shares in a biotech company, Genovo, which stood to gain from the research's outcome—shares that The Wall Street Journal later valued at $13.5 million, although Wilson maintains he did not make nearly this much. At the time Penn authorized Wilson's deal, internal Penn documents implicitly valued Wilson's stake in Genovo at approximately $28.5 to $33 million.

Jesse's death sparked two separate lawsuits: one by the family, who sued in tort, and one by the federal government, which framed alleged errors in the research trial as a civil False Claims Act violation. Both suits settled, with no public apologies or acknowledgement of wrongdoing in either case. The government refused to make public the documents it collected, despite requests from the family. Thus, in what is arguably the most famous conflict-of-interest case in medicine, we have known for a decade almost nothing about the nature of the financial stakes that Wilson, and Penn, had in the research's outcome, or why Penn authorized a researcher to hold such a substantial stake in that research's outcome. How this web of financial ties came to enmesh Jesse's trial is a subject worthy of exploration because it provides an important lens for evaluating two divergent visions about the role of money in research.

In 2009, the prestigious Institute of Medicine ("IOM") joined a growing chorus of voices that called for significant reforms to the rules governing disclosure of financial conflicts of interest. The IOM and other groups would presumptively bar nearly all equity stakes by researchers like Wilson. Although the IOM's view represents the dominant narrative about financial conflicts of interest, it is not the only one. One influential group urges that financial conflicts can never be removed from medical research and, indeed, should not be.

This Essay evaluates these polar positions by examining Jesse's participation in human research and his death. Drawing on new evidence from the documents collected in the Gelsingers' lawsuit, this Essay asks specifically whether new and better restrictions on financial conflicts of interest would have made a difference in Jesse's case and concludes that more robust restrictions would not have mattered. This Essay argues that rather...
than attempting to expunge financial interests from research, those interests should trigger significant, ongoing review of the affected clinical trials, much like the post-approval monitoring now used randomly by leading research institutions. Indeed, had Wilson's outsized financial stake triggered mandatory monitoring, people inside Penn likely would have stumbled upon the string of questionable decisions in Jesse's trial, including departures from the research protocol, long before those mistakes cascaded, culminating in Jesse's death.

Part II describes the research trial Jesse participated in and the lawsuits spawned by his death. In particular, Part II recaps the cavalcade of errors that the FDA says plagued the trial long before and up to Jesse's death, errors now largely acknowledged by Wilson. Part III reviews what the researchers told Jesse about the trial's risks, the results of prior animal studies, and the basic protections he would receive as a participant, and contrasts those disclosures with the frank disclosures approved by regulators at the trial's start. The approved disclosures candidly and explicitly revealed the death of animals in prior trials, vital information that was never shared with Jesse. Like the researchers' sterile description of those animal trials, Wilson's and Penn's financial interests in Jesse's trial were disclosed in a single bland sentence.

Part IV then follows the money, showing the nature and extent of Wilson's financial conflict of interest. This Part poignantly demonstrates that a lot of good people inside Penn sounded alarm bells about Wilson's hefty stake, to no avail. Although Penn's administration understood that Wilson's conflict of interest could be bypassed, it chose not to. Part IV also sketches the precautions suggested by Penn faculty to reduce risks to subjects participating in Wilson's research, such as creating a firewall between Wilson and crucial decisions in Jesse's trial. Part V then contrasts those proposed precautions with what actually transpired in Jesse's trial, noting the integral role Wilson played in many key decisions.

Part VI then evaluates the competing narratives about financial conflicts of interest through the lens of Jesse's trial. This Part ultimately concludes that even if Wilson had no financial interest in the trial's outcome, his desire for "recognition by [his] colleagues" and "successful competition for grants and the awarding of academic promotions and tenure" in the "competitive profession" of "academic medicine" likely would have driven him to make the same choices. Hence, deaths like Jesse's are unlikely to be avoided simply by banning financial conflicts. Instead, financial ties like Wilson's should trigger greater oversight of human trials and monitoring for human safety, an idea explored in Part VII.

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9 James M. Wilson, Lessons Learned from the Gene Therapy Trial for Ornithine Transcarbamylase Deficiency, 96 Molecular Genetics & Metabolism 151, 155 (2009) [hereinafter Lessons Learned].
II. JESSE’S ILL-FATED PARTICIPATION IN HUMAN RESEARCH

Jesse was three months past his 18th birthday when he died 10 years ago on September 17, 1999. This Part explains the impetus behind the human research trial in which Jesse participated, the structure of Jesse’s trial, and the principal figures conducting it. It then describes the pair of lawsuits that resulted, the novelty of the claims advanced, and how the settlement of both suits operated to shield from public view mistakes made in Jesse’s research trial.

A. JESSE’S RESEARCH TRIAL

Jesse had a rare disease, a liver deficiency called ornithine transcarbamylase deficiency (“OTCD”) that made it difficult for his liver to process proteins. If he ingested too much protein, the resulting nitrogen would overwhelm his system, fail to be processed as urea, and turn to ammonia, a poison to the central nervous system and the body.1

Jesse managed his OTCD with a special diet developed by the leading OTCD researcher, Dr. Mark Batshaw—a co-Principal Investigator for Jesse’s study. Batshaw, in fact, developed a medication that pulled Jesse out of a coma the December before Jesse enrolled in the trial. The coma was brought on when Jesse went off his diet. Aside from these periodic episodes after taking in too much protein, Jesse was a relatively healthy functioning adult—he had just graduated from high school, had a job, and was paying his parents rent.1

The idea behind the gene-therapy trial was to use a cousin of the common cold virus, an adenovirus or vector developed by Wilson, as a sort of “taxi” to deliver corrective genes to Jesse’s liver in hopes that they would express—relieving Jesse of the hold OTCD had on his life. The third player in Jesse’s research trial was the clinician who would oversee the injection of the vector into Jesse’s body, Dr. Steve Raper, a surgeon at Penn and Batshaw’s co-Principal Investigator. Wilson wore a second hat in the research trial. He was also a sponsor of the trial, meaning that an entity with which Wilson had

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11 Consent Form, supra note 8, at 2.
12 Paul Gelsinger, Statement at the Forum on Research Ethics, University of South Carolina School of Law (Apr. 5, 2001) (transcript on file with author) [hereinafter Gelsinger Remarks].
13 Id. at 4.
14 Id.
financial ties, Genovo, had the right to license any technologies developed in Wilson’s research.\textsuperscript{17}

Jesse participated in a Phase I clinical trial designed to test the safety of an intervention, not its efficacy, which usually gets tested in later phases.\textsuperscript{18} Jesse participated in a stair-step dosage trial designed to include 20 subjects in total. Jesse was participant OTC.019.\textsuperscript{19}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{stair-step-trial.png}
\caption{Stair-Step Trial}
\end{figure}

As Figure 1 shows, subjects on the lowest stair-step would receive 5,000 fold less of the vector used in prior animal trials in which monkeys and mice died.\textsuperscript{20} Those animals received a first generation virus, in contrast to the third generation virus that Jesse and other participants received.\textsuperscript{21} Unlike the first generation virus, the third generation virus lacked the portions that cause it to replicate in the body and to make people sick—that is, the parts that cause viral replication and viral pathogenesis.\textsuperscript{22}

The protocol for the trial provided that participants on the highest stair-step, as Jesse was, were to get 100 fold less of the vector than the animals received.\textsuperscript{23} After Jesse’s death, the Institute for Human Gene Therapy (“IHGT”), which Wilson directed at Penn, disclosed in documents filed with

\textsuperscript{17} Deborah Nelson & Rick Weiss, \textit{Hasty Decisions in the Race to a Cure?; Gene Therapy Study Proceeded Despite Safety, Ethics Concerns}, \textit{WASH. POST}, Nov. 21, 1999, at A01. See also infra Part IV.
\textsuperscript{19} Wilson, \textit{supra} note 9, at 152.
\textsuperscript{20} Mark L. Batshaw et al., \textit{Recombinant Adenovirus Gene Transfer in Adults with Partial Ornithine Transcarbamylase Deficiency (OTCD),} 10 \textit{HUMAN GENE THERAPY} 2419, 2429 (1999).
\textsuperscript{21} Wilson, \textit{supra} note 9, at 152.
\textsuperscript{22} \textit{Consent Form, supra} note 8, at 3.
\textsuperscript{23} Batshaw et al., \textit{supra} note 20, at 2429.
the FDA that Jesse received a considerably higher dose — 17 fold less of the vector than what the animals that died in a prior trial received.24

Jesse's ill-fated participation in the clinical trial began with a June 1999 visit by Jesse and his father, Paul Gelsinger, to Penn to see if Jesse was eligible to participate in the trial.25 During that visit, Steve Raper went through the Consent Form with Jesse and Paul.26 Jesse clearly understood that the trial, if successful, would provide no lasting benefit to him, but that it might pave the way to correcting the disease in newborn children. Paul Gelsinger explains that Jesse “signed on to help everybody and, hopefully, himself in the long run.”27 As Part III shows, neither Jesse nor Paul received the unvarnished truth about the results of prior animal studies, nor did they realize the magnitude of Wilson's potential gains from the research trial.

On September 13, 1999, Jesse was infused with the vector despite the fact that his ammonia levels fell outside the protocol's safety limit.28 Over the next four days, the vector took over Jesse's entire body, shutting down his vital organs. He died on September 17, 1999.

In the months following Jesse's death, the U.S. Senate and House of Representatives held hearings about his death, as did a host of federal regulators.29 The Washington Post also uncovered “[t]he first evidence that Wilson's company did in fact have a financial interest in the experiment,”30 raising questions about Wilson's motives. Ultimately, the FDA charged the researchers with protocol violations, misleading disclosures, and other mistakes in the trial. As the next Part explains, despite two separate lawsuits,
many of the questions raised by the FDA and others remained unanswered for nearly a decade.

B. A CASE OF FIRSTS

Jesse's death was a case of firsts. Jesse was the first person to die in a human gene-therapy trial.31 His family's lawsuit was also the first high-profile suit in which a family of a participant sued in tort to recover under a variety of new and creative claims.32 That suit was also the first to name a bioethicist, the world famous Arthur Caplan, director of Penn's Center for Bioethics, as a defendant based on the advice he gave the researchers regarding study design—which essentially urged testing the protocol on relatively healthy adults rather than dying infants.33 The family's lawsuit was also the first to spotlight a financial conflict of interest by a researcher, Wilson.34

Jesse's trial was also the first to trigger a lawsuit by the government in which it framed errors in a human subjects research trial as a civil False Claims Act violation, bringing to bear the crushing power of the penalties under that act.35 And Jesse's trial was the first to bounce researchers from human research for a period of years, albeit by agreement, and then to subject one of them, Wilson, to monitoring for a decade. As part of that settlement, Wilson was required to write an article about Lessons Learned from Jesse's trial as a condition precedent to being readmitted to human subjects research without restriction, another first.36 In 2009, almost a decade after Jesse's death, Wilson published his long awaited Lessons Learned article.37

For a case of firsts, one would think the public would have access to a storehouse of information about the underlying financial conflict of interest and the mistakes made in Jesse's trial, if any. Yet no public record exists of either proceeding because both settled.38 The family's lawsuit settled for an undisclosed amount less than 7 weeks after filing, before Penn even

34 See Wilson, supra note 26, at 248; Allen, supra note 33.
36 Id.
37 Lessons Learned, supra note 9.
38 See Caruso, supra note 5.
answered. The government’s suit settled before a civil charging document was even filed, burying for nearly a decade crucial details of that case.

Jesse’s death is worth re-examining, not only as a gripping piece of medical history, but also because other gene-therapy trial participants have also died. Moreover, because the rules governing conflicts of interest and disclosure of risks have largely remained unchanged since Jesse’s death, understanding what went wrong in Jesse’s trial can help us to improve the oversight of human subjects research. As the next Part documents, Jesse and Paul were told only partial truths about the risks Jesse would be taking by participating in the trial.

III. “DISCLOSURES” OF RISK AND BENEFIT

The disclosure form that Jesse actually saw and signed left a lot to be desired in terms of securing informed consent. The Consent Form alerts participants repeatedly that the trial is a non-therapeutic safety trial—that is, participants should not expect to gain anything from it. Jesse clearly understood he could not gain anything from participating in the trial. In fact, Paul often says he was a hero for participating precisely because he could not gain anything from it.

The Consent Form also discusses the risks of the trial, and lists three major risks to consider: “that receiving the virus now may prevent you from receiving a therapeutic dose of the virus in the future,” and that the virus may cause “an inflammation of your liver [or,] an immune response from your body which could damage the liver.” In fact, the latter is what killed Jesse: a massive immune system response. After Jesse’s death, Batshaw said it was like Jesse had fallen off of a cliff.

40 At least one other death has resulted in a gene-therapy trial. In 1998, researchers in Paris began gene-therapy trials on 11 children suffering from X-linked Severe Combined Immunodeficiency (X-SCID) or the “bubble boy” disease, a rare immune system disorder caused by a single gene defect. Four of the 11 children developed T-cell leukemia, one of whom died in October 2004. Weiss, supra note 10. "There is no doubt, in the Paris cases," the BBC reported, "that the leukemia was caused by the gene therapy, where the introduced gene was implanted next to, and switched on, an oncogene (a cancer causing gene)." Q&A: Gene Therapy Cancer Case, BBC NEWS, Dec. 18, 2007, available at http://news.bbc.co.uk/2/hi/health/7149460.stm.
41 Consent Form, supra note 8, at 3.
42 Gelsinger Remarks, supra note 12. Nonetheless, sprinkled throughout the Consent Form are references to evidence that “gene therapy for [OTCD] may be helpful.” Consent Form, supra note 8, at 3. The mixed messages about the therapeutic value of participating are problematic because they could mislead participants. See Nancy King, Defining and Describing Benefit Appropriately in Clinical Trials, 28 J. L., MED. & ETHICS 332 (2000).
43 Consent Form, supra note 8, at 7.
The risk discussion includes one of the three references in the 11 page Consent Form to the possibility of death. As Figure 2 shows, it notes that liver inflammation could be "life-threatening."

Although we believe the virus is safe, it is possible that it could cause an inflammation of the liver or hepatitis. It is even possible that this inflammation could lead to liver toxicity or failure and be life-threatening.

Figure 2

Elsewhere, as Figure 3 indicates, the Consent Form quantifies the risk of death from a biopsy, which may be needed during the course of the trial:

There is also a very small risk (1 in 10,000) of serious unpredicted complications which can include death.

Figure 3

Even though a remote risk, this statistic caused a heart-stopping moment for Jesse and Paul. Paul later recalled telling "Jesse that he needed to read and understand what he was getting into, that this was serious stuff."

After Jesse's death, The Washington Post and other news outlets widely reported that a predecessor of this form disclosed the deaths of animals in an earlier trial. Figure 4 shows what Jesse was told about those prior animal studies in the Consent Form.

The animals have not shown toxic effects to the liver or other body organs at the dosage of virus that is needed to transport the gene in this study. We have also tested the safety of this virus in monkeys and have not found toxicity at the doses being used in this study. (Higher doses were associated with liver inflammation [hepatitis] in animals.)

The maximum dose of virus we are proposing to use is still below that which has caused any severe problems in mice or monkeys.

Figure 4

In both discussions, the Consent Form sidesteps whether animals died in prior trials, electing instead to emphasize the lack of toxic effect at "the doses being used in this study." In good lawyerly fashion, neither lies about the deaths of the monkeys and mice—each just skirts the plain facts.

Two versions of the famed "monkey death" form were tucked in with the documents provided by a Penn whistleblower to the Gelsingers' attorney. As Figure 5 shows, the Institutional Review Board ("IRB"), which oversees research at Penn, approved the research on October 6, 1995, and cautioned the researchers that nothing could be changed in the disclosure form without

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46 Consent Form, supra note 8, at 7.
47 Id. at 8.
48 The animals have not shown toxic effects to the liver or other body organs at the dosage of virus that is needed to transport the gene in this study. We have also tested the safety of this virus in monkeys and have not found toxicity at the doses being used in this study. (Higher doses were associated with liver inflammation [hepatitis] in animals.)

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Nelson & Weiss, supra note 17; Nelson & Weiss, supra note 30, at 2 ("The original consent form reviewed by the RAC disclosed that monkeys died after receiving a high dose of a similar genetically-altered virus carrying the OTC gene. Yet the monkey deaths had disappeared from the consent form that Jesse received, which we got from Penn after obtaining Jesse's father's permission.").
49 Consent Form, supra note 8, at 3, 7.
Amendments: If you wish to change any aspect of this study, such as procedures, the consent forms, or the investigators, please communicate your requested changes in writing to the Associate Director for Regulatory Affairs. The new procedures cannot be initiated until Committee approval has been given.

Figure 5

Figure 6 presents excerpts from a disclosure form dated 10/2/95 by “ser,” presumably co-principal investigator Steve Raper, making it very likely that this is the form the IRB saw and approved. The 10/2/95 disclosure form bluntly referenced the death of both monkeys and mice, as Figure 6 shows.

In mice and monkeys high doses of the virus have been associated with evidence of liver inflammation (hepatitis), hepatic necrosis and death.

Figure 6

Figure 6 makes clear that the researchers were capable of saying that animals died in earlier studies and that participants could die too. But the Consent Form Jesse received dropped these bald statements in favor of the claim that animals did not show toxic effects at the dosage "used in this study."

In contrast to the Consent Form's scant attention to animal deaths in earlier trials, the Consent Form Jesse signed devotes ample attention to all the things that will reduce the risks to Jesse, whatever those risks are. The Consent Form explains that the trial is a stair-step trial, with escalating doses. It assures the reader that if something arises, “we should be able to identify any problems early and start treatment.” It also promises to disclose the effects experienced by prior participants. Crucially, it says “[i]f there are serious side effects the study will be stopped.”

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62 On November 21, 1995, the researchers responded to comments by members of the Recombinant DNA Advisory Committee (“RAC”), which together with the FDA exercised oversight authority at the federal level. Memorandum from Mark Batshaw, Steven Raper, & James Wilson, Univ. of Pennsylvania Health Sys., to Nelson Wivel (Nov. 21, 1995) (on file with author). In one part of that correspondence, the researchers suggest new text for the Consent Form in response to the RAC comments. Id. Crucially, the disclosure of monkey and mice deaths is identical to the disclosure on the 10/02/95 form. Consent Agreement for Recombinant Adenovirus Gene Transfer in Adults with Partial Ornithine Transcarbamylase Deficiency at 7 (1995) (on file with author) [hereinafter "1995 Consent Form:].
63 1995 Consent Form, supra note 52, at 4.
64 Consent Form, supra note 8, at 3. The IRB that exercised regulatory oversight for Jesse’s trial seems to have done everything right—they policed the disclosure, they told the researchers not to change it without permission—but then the IRB trusted that the researchers would respect the rules. The mandatory post-approval monitoring suggested in Part VI presumably would have uncovered this important change in the approved disclosure to participants.
65 See id. at 4-6.
66 Id. at 7.
67 Id.
researchers promised to make all these disclosures in writing to participants so they can reconsider participating as new information comes up—something that Paul Gelsinger says did not happen.\(^\text{58}\)

**SIGNIFICANT NEW FINDINGS**

Any significant new findings developed during the course of the study that could affect your willingness to continue participating in the study will be provided, in writing, to you. You will be given a chance to ask questions about this new information before continuing in the study. In such circumstances, we would revise the informed consent document and offer you an opportunity to reconsider your participation.

**Figure 7**

Finally, Wilson's ties to the research, as well as Penn's, get disclosed in a single bland sentence, reproduced in Figure 8.

**SPONSOR INFORMATION**

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.

**Figure 8**

The U.S. Government's civil suit for false claims rested in part on the failure to obey the protocol's adverse event stopping rules and to give notice, as promised in the Consent Form.\(^\text{61}\) Because both the government's suit and family's suit both settled, the FDA's charges of mistakes went largely unanswered by the researchers for nearly a decade. That changed in 2009 with Wilson's publication of his *Lessons Learned* article, a condition precedent to being readmitted to human subjects research without restriction.\(^\text{62}\)

Thus, the FDA charged that the three researchers blew through clinical stop signs under the protocol, pointing to Grade 3 toxicities on stair-steps below Jesse. This, the FDA charged, should have stopped the trial but did not.\(^\text{63}\) Wilson concedes in his *Lessons Learned* article that there is substance

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\(^{58}\) *Gelsinger Remarks*, supra note 12.

\(^{59}\) *Consent Form*, supra note 8, at 10-11.

\(^{60}\) *id.* at 11.


\(^{62}\) Interview with David Hoffman, Former Assistant U.S. Attorney, in Phila., Pa. (June 6, 2008).

to this charge. As he explains, "[t]he clinical trial progressed through the first five cohorts, although toxicity was indeed observed," which included "fever and flu-like symptoms with some transient laboratory abnormalities."\(^{64}\)

The FDA also alleged that on the day Jesse was infused, his ammonia levels tested outside the limits established by the protocol.\(^{65}\) As Wilson now acknowledges, while Jesse's serum ammonia levels on the day of the infusion "fluctuated around the threshold of 70 μM" - fluctuation the researchers did not find clinically significant - the protocol "was not written to include clinical relevance of metabolic measures in assessing inclusion criteria, providing credence to the FDA's concerns."\(^{66}\)

Compounding these errors, the FDA charged that changes were made to the protocol and Consent Form without permission from the relevant oversight bodies at Penn and in the federal government.\(^{67}\) In his Lessons Learned, Wilson describes the protocol as a "living document with changes occurring in real time."\(^{68}\) He accedes that in one set of revisions, the researchers increased the threshold for subjects' serum ammonia from 50 to 70 μM. Wilson does not directly acknowledge changes to the disclosure about animal deaths in the Consent Form but, as Part V explains, Wilson says that all three researchers had a hand in deciding precisely what participants would be told.

The loose management of Jesse's trial leads most people to wonder why it occurred, and more particularly whether Wilson's giant-sized financial stake played any role. Before delving into those questions, the next Part charts how it came to pass that Wilson had such a substantial stake in the outcome of Jesse's trial.

IV. MAKING SENSE OF THE MONEY

The federal conflict of interest and disclosure rules have not changed materially in the decade since Jesse's death. These rules require researchers to disclose significant financial relationships—defined as $10,000 in equity, salary or any other thing of value or 5 percent or more of the shares in an

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\(^{64}\) Lessons Learned, supra note 9, at 152.

\(^{65}\) Letter from Masiello to Wilson (Nov. 30, 2000), supra note 63, at 5; Lessons Learned, supra note 9, at 154.

\(^{66}\) Lessons Learned, supra note 9, at 154.

\(^{67}\) Letter from Dennis E. Baker to Wilson, supra note 61.

\(^{68}\) Id.
entity—to the institution receiving the grant. That institution, Penn, must eliminate or manage the conflict by the time grant funds are distributed.

The financial arrangement between Wilson, Penn, Genovo, and Genovo’s minority owner but super-majority shareholder, Biogen, was a complex one, as Figure 9 illustrates.

![Figure 9](image)

Essentially, Wilson directed a huge institute established at and wholly owned by Penn, the Institute for Human Gene Therapy, that in its heyday

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69 Federal regulations define a "Significant Financial Interest" as "anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights)." 42 C.F.R. § 50.603 (2008). The definition excludes:

(5) An equity interest that when aggregated for the Investigator and the Investigator’s spouse and dependent children, meets both of the following tests: Does not exceed $10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent more than a five percent ownership interest in any single entity; or

(6) Salary, royalties or other payments that when aggregated for the Investigator and the Investigator’s spouse and dependent children over the next twelve months, are not expected to exceed $10,000.

Id.

70 Wilson, supra note 27, at 244 (adapted with permission from Aspen Publishers).
claimed over 200 affiliated faculty. IHGT housed intellectual property developed by Wilson while at Penn and at the University of Michigan, where he was prior to joining the faculty at Penn. Penn entered into a sponsored research agreement ("SRA") with Genovo, the biotechnology company that Wilson established while at Michigan, pursuant to which Penn would grant to Genovo the rights to license the existing Wilson technologies, together with the option to license new technology.\(^7\) Wilson held varying amounts of stock in Genovo, depending on who was in and out of Genovo at a given time.

The question presented to Penn's conflict of interest committee was whether to allow Wilson such a big share in exchange for Genovo and the entity controlling it, Biogen, doing sponsored research at Penn. Under the SRA, Genovo would commit $21 million over 5 years to fund research in "Dr. Wilson's laboratory" and give Penn 5% of the equity in Genovo.\(^7\) In exchange, Genovo would receive the right to license existing and new Wilson technologies.\(^7\) Wilson would not manage or otherwise control decisions made by Genovo.\(^7\)

Although Wilson's stakes in Genovo would be valued at $13.5 million by The Wall Street Journal on the date that Genovo was acquired by another company, Penn contemplated that Wilson's shares may have been even more valuable.\(^7\) The memo excerpted in Figure 10 from Kathleen Denis, Director of the Center for Technology Transfer at Penn, to the chair of the conflict of interest committee implicitly priced Wilson's stake in the tens of millions of dollars. The memo noted that earlier in the same year Biogen purchased its 38% share of Genovo at a cost of $36.2 million over five years, yielding a value of roughly $952,361 for each 1%.\(^7\) Denis notes that Wilson will have a "large personal stake, approximately 30-35%" of Genovo.\(^7\) If sold on the same terms as Biogen's purchase, this would mean a deal for Wilson in the neighborhood of $28.5 to $33.3 million.\(^7\)

\(^7\) See Memorandum from Denis, supra note 3.
\(^7\) See Conflict of Interest Standing Committee Report on Genovo Case, Final Draft, from Neal Nathanson, Chair, CISC, to Barry Cooperman, Vice Provost for Research (Apr. 5, 1995) (on file with author) ("This SRA will be used only to fund work in Dr. Wilson's laboratory and not in the laboratories of other members of his department (Department of Molecular and Cellular Engineering) or the laboratories of members of the Institute for Human Gene Therapy.").
\(^7\) See Memorandum from Denis, supra note 3.
\(^7\) Nelson & Weiss, supra note 17.
\(^7\) See Letter from Barry S. Cooperman, Vice Provost, Research, to James Wilson (June 29, 1995) (on file with author).
\(^7\) See Hensley, supra note 2.
\(^7\) See Memorandum from Denis, supra note 3.
\(^7\) Id.
\(^7\) Id.
The most recent Biogen/Genovo term sheet shared with Penn shows Biogen investing $36.2 million over the next five years in exchange for 38% of Genovo's equity and commercialization rights.

Dr. Wilson will have a large personal share (approximately 30-35%) although approximately one-half of this stock has been placed in a trust for his children.

Whether to authorize a stake of this magnitude and what it would mean for human safety were the questions presented to Penn's Conflict of Interest Standing Committee (“CISC”), the body charged with overseeing financial conflicts at Penn.80 The CISC had numerous members. Its membership included Arthur Caplan, who later advised the researchers on study design. Caplan recused himself from the CISC's deliberations because of a conflict of interest or the appearance of one—namely, that Wilson chaired the department in which Caplan had tenure.81

The CISC also included faculty from around the university, including the Medical School and the Law School. The CISC ultimately reported to Barry Cooperman, Penn's Vice Provost for Research, who reported to the provost and the president at the time, Judith Rodin. The CISC met 4 times in 4 months. At one meeting they grilled Wilson and asked hard questions.82

79 See Memorandum from Denis, supra note 3.
80 See University of Pennsylvania, CISC Procedures (April, 1995), attached to Memorandum from Neal Nathanson to CISC Members (May 7, 1995) (describing the functions of the CISC) (on file with author).
82 Memorandum from Dale Lombardi, Sec'y, CISC, to CISCI Members (Mar. 28, 1995) (on file with author) (draft minutes of Mar. 13, 1995 meeting).
Nonetheless, at the end of this long process, the CISC emerged with nearly the same deal that was proposed at the beginning. Notwithstanding this, Penn's process was a good one from start to finish. Penn obtained advice from a top health law firm. The CISC thought long and hard about the protections for participants. As Figure 11 shows, the CISC composed a list of issues raised by Wilson's deal in one of its early meetings.

CENTER FOR TECHNOLOGY TRANSFER

MEMORANDUM

To: CISC MEMBERS
From: Dale M. Lombardi
Date: March 3, 1995
Subject: DRAFT MINUTES OF FEBRUARY 6, 1995 MEETING

5. How can Dr. Wilson and the University avoid liability for any damages if a patient died from any products produced or studied at the University?

15. Once a research course has been chosen, what steps will be taken to assure the University that the results of studies will not be biased by the financial interests of Dr. Wilson or his staff?

16. Since Dr. Wilson's research efforts will be directed towards the solution of a problem in which he has a financial interest in the outcome, how can Dr. Wilson assure the University that he will not be conflicted when making decisions that could have an impact on either Genovo, Biogen or the further development of his intellectual property?

Figure 11*

Question 5 is especially prescient. It asked how Wilson and the University could avoid liability for any damages if a participant died in a trial. Ironically, this question gets dropped from the final minutes of that meeting. Questions 15 and 16 also zero in on the impact of Wilson's stake for the university and others, asking in particular about concrete steps to ensure that funded studies are not biased by Wilson's interests.

In the March 13 meeting at which Wilson appeared, one CISC member, Dr. Jim Eberwine, asked the $64,000 question. As Figure 12 shows, he asked Wilson whether Wilson will be involved "in the evaluation of clinical data" in

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83 See Memorandum from Denis, supra note 3.
84 Memorandum from Dale Lombardi, Sec'y, CISC, to CISC Members (Mar. 3, 1995) (on file with author) (draft minutes of Feb. 6, 1995 meeting).
85 Memorandum from Dale Lombardi, Sec'y, CISC, to CISC Members (Mar. 20, 1995) (on file with author) (final minutes of Feb. 6, 1995 meeting).
funded trials. Wilson responded that he “will not be involved in the design or evaluation of the clinical trials.”

Dr. Eberwine raised the issue of Dr. Wilson's involvement in the evaluation of clinical data developed from patient trials. Dr. Wilson answered that he will not be involved in the design or evaluation of the clinical trials. However, he reserved the right to be an author for any manuscripts that evolve out of any trials.

Figure 12

Far from a firewall like that contemplated by Dr. Eberwine and the CISC, Part V shows that Wilson was hip deep in decisions affecting Jesse's trial. Indeed, Wilson places himself in the room when the researchers made key decisions throughout Jesse's trial, such as what disclosures to make in the Consent Form Jesse signed.

Ultimately, the CISC determined that it will need “unusual circumstances” in order to meet outside counsel's recommendations for approving a financial conflict of interest on this scale. CISC member and law professor Seth Kreimer drafted a memorandum with a number of proposed findings. The findings that might support unusual circumstances included the possible benefit of Wilson's research to the public, the possibility for opening a wide range of research at Penn, the need to get a timely start on research in a rapidly changing scientific environment, the fact that nascent technologies developed by Wilson were already under license to Genovo and that Wilson's involvement was important for the new research's likely success, together with the likely lack of available funding from other sources, like NIH. Kreimer ended the list with what he saw as the crucial question, reproduced in Figure 13 – namely, whether the draft findings warranted approval of Wilson's deal.

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86 Memorandum from Lombardi to CISC Members, supra note 82.
87 Id.
88 Memorandum from Seth Kreimer, Prof. of Law, Univ. of Pa., to Dale Lombardi, Sec'y, CISC (May 18, 1995) (on file with author).
89 Id.
90 Id.
The residual question for the Committee is, whether these findings are unusual enough to suggest that it is necessary for Dr. Wilson to get a large equity position and that Genovo be the corporate sponsor of the research as opposed to simply justifying the institute's research being funded directly by Biogen?

Figure 13

The margin comments made in Figure 13 come from an ex-officio member Carol Grande, who represented Penn's Center for Venture and Industry Relationships. She suggested that the minutes drop Kreimer's residual question.91

Whether the CISC agreed on Kreimer's proposed findings became hotly disputed, as the letter from another member, Professor Louis Girifalco, drives home.92 Reproduced in Figure 14, Girifalco's letter relayed his concern that the CISC never agreed on unusual circumstances findings, yet alone voted to accept those findings. For him, the factors surrounding the Genovo case were not "very different from those involved in very many, if not all, high quality research programs," a view he believed others shared.93 Because the findings were "not in accord with what transpired," he asked that the minutes be corrected.94

I am somewhat confused by the draft minutes of CISC for May 18, 1995 and June 15, 1995 that you just sent me. I am particularly concerned about the references to "unusual circumstances" in these minutes.

The minutes give the impression that our committee has carefully defined the term "unusual circumstances" and that this definition was applied to the Genova project. In fact, the May 18 minutes state that the committee voted to accept findings of "unusual circumstances" for this case.

91 Id.
92 Fax from Carol Grande, Dir., Ctr. for Venture & Indus. Relationships, to Dale Lombardi, Sec'y, CISC (June 8, 1995) (attached to the Kreimer Memo, supra note 88) (on file with author).
93 Fax from Louis Girifalco to Dr. Barry Cooperman, Vice Provost, Research (July 12, 1995) (on file with author).
94 Id.
95 Id.
THE DEATH OF JESSE GELDSINGER

This is not in accord with what transpired. The Committee did not generate any findings of "unusual circumstances", and my recollection of the vote is that it referred to process, not substance.

The minutes do not adequately reflect the concern some members of the Committee had with respect to the meaning of "unusual circumstances". I want to now repeat my statement that there was nothing in the discussion of the Genova case that led me to believe that the factors involved in the Genova case were very different from those involved in very many, if not all, high quality research programs. I believe that there were other members of the Committee that shared my views.

Figure 1496

When Girifalco's concerns were not addressed, he resigned.97 As Figure 15 shows, he reiterated his concern that the notion that "the Committee voted to accept findings of 'unusual circumstances'... was an error."98

If you will examine the Committee minutes, you will note that they state that the Committee voted to accept findings of "unusual circumstances" with respect to the proposed Genova arrangements. This was an error. The Committee did not vote on this. I wrote a letter to the Chairman and the Secretary of the Committee requesting that the minutes be corrected.

The minutes were not corrected; instead my letter was simply attached to the minutes. This can give the appearance that I was merely expressing a minority view that is open to interpretation and not that the minutes were in error.

Figure 1599

Throughout the process of clearing Wilson's financial stake in Genovo, concerns like Girifalco's continued to crop up. At the eleventh hour, Associate General Counsel Robert Terrell annotated the final report delivered to Vice Provost Cooperman.100 Terrell observed in his own handwriting:

Because the potential conflicts stem largely from Dr. Wilson's equity holdings in Genovo, it seems to me that what needs to be explained is not the benefits to the University from the SRA, since presumably University interests are advanced by most SRAs, but what University interests are advanced by allowing Dr. Wilson to participate as proposed, i.e. a substantial equity holder in a sponsor that may benefit from the results of the research. I'm not sure the proposed findings really address this issue. Is the deal only possible if Dr. Wilson holds a substantial equity position in Genovo? Why?101

Terrell was not alone in having lingering concerns. Paul Soven, a CISC member, also found the draft "unusual circumstances" not compelling.102 He said "it's a good try but Kreimer's residual question is very cogent. Is it

96 Id.
97 Fax from Louis Girifalco to Dr. Barry Cooperman, Vice Provost, Research (July 18, 1995) (on file with author).
98 Id.
99 Id.
100 Comments on draft CISC recommendations from Robert Terrell, Assoc. Gen. Counsel, Univ. of Pa., to Barry Cooperman, Vice Provost for Research (Apr. 5, 1995) (on file with author).
101 Id. at 2-3.
102 Fax from Paul Soven, Member, CISC, to Dale Lombardi, Sec'y, CISC (May 31, 1995) (on file with author).
possible that Biogen simply will not come in unless Wilson has a very strong
stake in the matter?\footnote{103}

Others questioned what “unusual circumstances” even meant as to
Wilson’s deal. In a fax dated June 20, 1995, Chair Neal Nathanson told Vice
Provost Barry Cooperman that “[t]he term ‘unusual circumstances’ appears to
mean different things to different members of the committee, and I have the
impression that these differences will remain an area of ambiguity. It’s a bit
like the way the supreme court has chosen to interpret a key phrase in the
constitution differently in different eras, depending on who was writing the
opinion.”\footnote{104} Nathanson questioned not only the ill-defined justification, but
the deal’s wisdom: “[S]ome members of the CISC clearly have doubts whether
the terms which were negotiated between the School of Medicine and Genovo
were the best terms which the institution could obtain or even whether they
were acceptable terms. Particular concern was expressed . . . whether the
institution should have insisted that the sponsored research agreement be
made between Biogen and Dr. Wilson rather than Genovo and Dr. Wilson.”\footnote{105}

Despite a stream of advice that Penn could simply bypass Wilson’s
conflict, Penn chose not to. It approved Wilson’s stake on June 25, 1995,
subject to Wilson’s acceptance of 16 conditions.\footnote{106a} The bulk of these
restrictions policed the relationship between Wilson and Genovo, forbidding
him to serve in a management role or on the Scientific Advisory Board for
Genovo or Biogen, capping his equity holdings in Genovo at 30%, limiting his
consulting (for all organizations, including Genovo) to “one day in seven,” and
prohibiting him from receiving compensation when consulting with Genovo
or Biogen.\footnote{106b} The letter agreement also required Wilson to disclose his
financial interests in “publications and public presentations” and to all “current”
and “prospective” members of Wilson’s lab, to be available “to discuss with members of your laboratory any concerns or questions ...
regarding Genovo-sponsored research,” and to provide information annually
to lab members about an oversight committee that Penn established.\footnote{106c} As to
the conduct of research trials funded by Genovo, the letter agreement directed
Wilson to:

\begin{quote}
Avoid direct participation in the conduct of clinical studies in
which Genovo or Biogen has an interest. You are allowed to
participate in the design of such studies but shall not be
responsible for the analysis of data resulting from such studies.\footnote{106d}
\end{quote}

\footnote{103 Id.}

\footnote{104 Fax from Neal Nathanson, Chair, CISC to Barry S. Cooperman, Vice Provost for
Research, CISC (June 20, 1995) (on file with author).}

\footnote{105 Id.}

\footnote{106 Letter from Cooperman to Wilson, supra note 74.}

\footnote{107 Id.}

\footnote{108 Id. Two provisions reiterated existing Penn policies: that human research be approved
by Penn’s IRB and that animal research be approved by the relevant oversight body. Id. Two
other provisions required Wilson to forego the “inventor’s share of equity” and “inventor’s
share of royalties” that Wilson would otherwise have received. Id.}

\footnote{109 Id.}
Thus, the letter agreement between Wilson and Penn created a firewall between Wilson and the management of Genovo but a flimsy barrier between Wilson and the management of trials like Jesse’s.

Of course, the mere possibility of Wilson’s participation in key decisions in Jesse’s trial does not mean that he participated nor does it mean that the possibility of significant financial gain precipitated any particular act or mistake. The next Part examines Wilson’s role in crucial decisions made during Jesse’s clinical trial.

V. WILSON’S ROLE IN JESSE’S CLINICAL TRIAL

One overarching question about how to regulate financial conflicts of interests going forward is whether the money matters at all. Wilson’s own admissions in his Lessons Learned article provide the best evidence for what he actually did in Jesse’s trial and for what he might have done had no money been at stake. In that article, Wilson acknowledged that he founded “a biotechnology company focused on gene therapy while being directly involved in gene-therapy clinical trials as a sponsor of the respective [Investigational New Drug].” Not only did the “juxtaposition of these two facts, independent of their connection, raise[] the perception of a potential financial conflict,” but “any clinical success would likely bolster investor support for the commercial developments of gene therapy that could enhance the value of most existing gene-therapy companies, including Genovo.” Thus, as Wilson acknowledges now, Genovo’s success might well have lined Wilson’s pockets.

Still, to make the claim that the possibility of financial gain mattered in Jesse’s trial, one would have to believe that Wilson would have made different choices, with different outcomes, had Wilson not had the possibility of financial reward. A 2006 book on medical research, What the Doctor Didn’t Say: The Hidden Truth About Medical Research, observed:

There is little reason to think that [Wilson’s] financial interests had anything to do with the specific “wrong things” that were considered to have taken place in [Jesse’s] study. For example, some of the steps taken in enrolling Jesse in the study appeared to violate procedures required by the protocol. But there’s no specific evidence linking these decisions to Dr. Wilson. More likely they were made by more junior members of the research team ...

In the weeks after Jesse’s death, the idea of distance between Wilson and Jesse’s trial itself seemed a good one. As a sponsor, Wilson would have sat high above the clinical fray. The Washington Post reported that, according to insiders, Wilson “went to great pains to ensure that his business interests

\[10^*\] Wilson, supra note 9, at 155.
\[11^*\] Id. (noting that “in this kind of situation, perception can quickly become reality”).
\[12^*\] Id.
would not influence his judgment during [Jesse’s trial]. . . . [H]e gave Raper control over medical and patient care decisions.\textsuperscript{114}

But Wilson’s own account of how the researchers ran Jesse’s trial disproves any notion of Wilson’s isolation from the trial’s conduct. According to Wilson, responsibilities for Jesse’s trial “were distributed amongst the three physician-scientists . . . . Decisions were made in the context of ‘team meetings’ with all constituencies present.”\textsuperscript{115} Wilson lauded the value of such a collaborative approach, arguing it “provided transparency for key decisions and invited input from all members of the group,”\textsuperscript{116} including him.

Among other key decisions, Wilson participated in honing the content of the Consent Form, which, like other decisions, was hashed out in a team meeting.\textsuperscript{117} Specifically,

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 additional primate data on the ongoing OTCD study.\textsuperscript{118}

In light of the stark changes to the Consent Form’s discussion of earlier animal deaths, outlined in Part II above, this is a significant admission. Someone, at some point, removed the bald acknowledgement—approved by the IRB and the RAC—that animals had died in prior trials and substituted instead the carefully worded, but potentially misleading, disclosure made to Jesse and Paul.\textsuperscript{119} Someone somewhere decided to change the Consent Form without, according to the IRB and the RAC after Jesse’s death, sharing that fact with the regulators charged with policing the consent process.\textsuperscript{120} By his own account, Wilson was intimately familiar with the Consent Form and with the content of the disclosure to the RAC and presumably the IRB\textsuperscript{121} and helped to make the call about what to tell participants like Jesse.

Still, there is every reason to believe that the outcome of Jesse’s trial ould have been the same even if Wilson had had no monetary interest at stake. In his Lessons Learned, Wilson notes that in the “competitive profession” of “academic medicine . . . the primary measure of success [is] recognition by your colleagues of your research accomplishments.”\textsuperscript{122} Such recognition “is critical to sustaining one’s research agenda through the successful competition for grants and the awarding of academic promotions and tenure.”\textsuperscript{123}

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\textsuperscript{114} Nelson & Weiss, supra note 17.
\textsuperscript{115} Id.
\textsuperscript{116} Id.
\textsuperscript{117} Id.
\textsuperscript{118} Id.
\textsuperscript{119} Nelson & Weiss, supra note 30, at 1, 2 (“The original consent form reviewed by the RAC disclosed that monkeys died after receiving a high dose of a similar genetically-altered virus carrying the OTC gene. Yet the monkey deaths had disappeared from the consent form that Jesse received, which we got from Penn after obtaining Jesse’s father’s permission.”).
\textsuperscript{120} See Nelson & Weiss, supra note 17.
\textsuperscript{121} See supra footnote 52 and accompanying text.
\textsuperscript{122} Lessons Learned, supra note 9, at 155.
Since Jesse's death, Wilson has maintained consistently that money does not motivate researchers like him. As he told The Washington Post two months after Jesse's death, "To suggest that I acted or was influenced by money is really offensive to me. I don't think about how my doing this work is going to make me rich. It's about leadership and notoriety and accomplishment. Publishing in first-rate journals. That's what turns us on. You've got to be on the cutting edge and take risks if you're going to stay on top."

Wilson's own ego and professional pride, his lust for academic recognition and advancement, all suggest that the drivers for him went far beyond his shares in Genovo.

As the next Part explains, Wilson's ambition and complex motivation provides a useful test of the two dominant narratives about financial conflicts – namely, that the best way to manage financial conflicts is to bar them entirely and the contrary view that we would be foolish to eliminate such ties.

VI. COMPETING NARRATIVES ABOUT FINANCIAL TIES

The debate about financial conflicts of interest in human subjects research has been dominated by two competing narratives—that researchers' financial ties advance science by drawing new streams of money in an era of shrinking public support for human subjects research, and the competing idea that financial ties exert a "corrosive effect" on researchers' judgments.

As the most famous financial conflict of interest case in recent memory, Jesse's trial provides an important lens for evaluating these conflicting visions about the role of money in research. This Part concludes that neither narrative accurately captures the complexity of the researchers' interests and motivations during Jesse's trial, or the complexity of the financial deal itself.

123 Id.
124 Nelson & Weiss, supra note 17.
125 Just as the fact of a conflict does not prove an impact on judgment, neither does the fact of participation by Wilson tell us whether better or different rules would have made a difference in Jesse's trial. This kind of proof will likely never be present when a trial ends badly, unless the conflicted researcher issues a mea culpa.
126 Institutional conflicts of interest have also come under fire. Universities as a group are the single largest patent holder in the world, and make money as a result of translating research of individual faculty into the marketplace. Presumably, if the adenovirus developed by Wilson performed well, Penn would have gained directly, either by licensing the virus or as a result of its equity interest in the licensing body, here Genovo. Thus, while the institutional conflict of interest would likely have been present in any arrangement that Penn authorized, the individual conflict of interest would not have been nearly as pronounced if Penn had required Wilson to divest his shares in Genovo. Cf. supra Part IV (discussing financial conflicts of interest).
127 Concerns for patient trust comprise a third narrative. See, e.g., Kevin P. Weinfurt et al., Effects of Disclosing Financial Interests on Attitudes Toward Clinical Research, 23 J. Gen. Internal Med. 862, 864 (2008) (finding in a survey of adults suffering from diabetes or asthma that disclosures of financial conflicts "were associated with some respondents trusting the researchers less, although trust among some respondents increased," and observing that the "findings regarding trust area important given how central trust can be to participation in research and to public acceptance of research findings, and considering the need to ensure that the clinical research enterprise merits the trust that participants confer on it.").
A. Industry Funding is Essential?

Consider first the pro-industry-funding position. The American Council on Science and Health ("ACSH") issued a position paper in 2008 signed by a prestigious group of members, which included Arthur Caplan. In it, ACSH sees "very real harm that can result from limiting industry/university collaborations." It maintains that "the collaboration between science and industry has been threatened by the development of a movement that proposes to end or drastically limit such cooperation on the grounds that it involves unacceptable conflicts of interest."

In ACSH's view, bans go too far because two "mechanisms currently in place to protect the integrity of scientific research," peer review and disclosure, suffice to prevent abuses. For example, before a paper is published in a scientific journal, the findings are reviewed anonymously by other experts. This "ensures that all research published in peer-reviewed journals has undergone systematic scrutiny before publication," exposing flaws in the research design "attributable to a wide variety of causes, not just those linked to conflicts of interest." These journals also "require the authors of submitted papers to disclose any financial interests relevant to the work being submitted, as well as the source of funding for the research." Such disclosure rules, the ACSH maintains, are better than "prohibiting those with potential conflicts of interest from engaging in certain types of professional activity."

At least in Jesse's trial, ACSH's confidence in these mechanisms as checks on the potential for abuse seems misplaced. Wilson published papers about the trial both before Jesse's death and after. One paper published after Jesse's death discloses Wilson's conflict in an acknowledgment after the body of the paper in this way: "Dr. Wilson previously received support from Genovo, Inc., a company in which he holds equity." This disclosure does not alert the reader to the nature or degree of Wilson's financial interest in Genovo or to Wilson's role in the conduct of the published study and says nothing about any opportunities for bias or an impact on Wilson's judgment. Like this unadorned statement, the disclosure made to Jesse in the Consent Form, which arguably represented the state of the art at the time, blandly references

...
"a financial interest in a successful outcome." Like the author disclosure, a "financial interest" could encompass a $1,000 payment for each subject enrolled, as occurs with many trials sponsored by pharmaceutical companies, or it might encompass the tens of millions of dollars that Penn implicitly contemplated Wilson holding in its December 15, 1994, memo. Empirical studies of disclosure show that most readers see these financial tethers as very different conflicts. But each kind of conflict would result in the same one-sentence disclosure without more. Because negligible ties trigger the same disclosure as the possibility of millions, it seems unlikely that mere disclosure can serve as a meaningful check on conduct in the funded trial.

Neither does a one-sentence disclosure alert participants or peer reviewers to the ground rules imposed by the institution on the researcher's participation or to whether the researcher complied with those ground rules. The possibility of clouded judgment stems not only from a researcher's financial interest, but from the researcher's precise role in the trial. CISC member Jim Eberwine contemplated a firewall between Wilson and any decisions made in the trial, a constraint that Penn significantly relaxed when it instructed Wilson to "[a]void direct participation in the conduct of clinical studies in which Genovo or Biogen has an interest." Wilson acknowledges in his Lessons Learned that he shared significant "responsibilities for the protocol"—decisions that have a direct bearing on what happened to participants in the trial. For example, a key requirement for enrolling subjects in the trial involved "a measurement of serum ammonia." In the course of multiple revisions to the protocol, this "threshold had been increased from 50 to 70 µM." Had the firewall envisioned by Eberwine been in place, Wilson would have played no role in the decision to change this critical indice in the protocol. By contrast, it appears that Penn's letter agreement with Wilson allowed precisely this type of participation by him in key decisions that a reasonable person would foresee impacting real people.

On a deeper level, ACSH's core claim that financial conflicts should be overlooked because of the need to draw money to research is flawed as to Jesse's case. Person after person inside Penn charged with evaluating Wilson's hefty stake recognized that Wilson's deal may not have been necessary to securing the sponsored research agreement. As they pointed out, Penn could simply have run the SRA from Biogen to Penn, bypassing

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136 Consent Form, supra note 9, at 11.
137 Weinfurt et al., supra note 127, at 861.
138 See Memorandum from Denis, supra note 3.
139 When asked, potential research subjects view equity ownership as much more problematic than receiving per capita payments or other financial conflicts. Weinfurt et al., supra note 127, at 863; Lindsay A. Hampson et al., Patients' Views on Financial Conflicts of Interest in Cancer Research Trials, 355 NEW ENG. J. MED. 2330, 2336 (2006).
140 Letter from Cooperman to Wilson, supra note 74.
141 Lessons Learned, supra note 9, at 154.
142 Id.
143 See supra Part V (discussing comments by the Associate General Counsel Robert Terrell and the Conflict of Interest Standing Committee chair Neal Nathanson, among others).

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Genovo and Wilson's conflict entirely. If Penn had structured the SRA between Biogen and Penn, Wilson presumably still would have participated in funded research but would not have had an equity interest in the outcome. If Penn had taken this approach, it still would have had entered into a SRA and received all the biotech dollars that flow from that—demonstrating that funding and conflicts need not always go hand-in-hand. Indeed, Jesse's trial exposes this "trade-off" as a false choice.

B. CONFLICTS CORRUPT JUDGMENT?

Anchoring the other end of the spectrum from ACSH is the 2009 IOM report on conflicts of interest. In it, the IOM states that "individuals generally [should] not conduct research with human participants if they have a significant financial interest in an existing or potential product or a company that could be affected by the outcome of the research." The IOM receives considerable support for this position from study participants themselves. For instance, when a financial conflict of interest is present, study participants worry about "data integrity" and "conflicts of interest" as well as "money's potential corrupting influence."

As hawkish as the IOM is about financial conflicts, it would nonetheless make some limited allowance for clinical investigators to hold equity interests. This would occur only when the clinical investigator's "participation is determined—after careful assessment—to be necessary for the safety, reliability, or validity of the research." Even then, the IOM would require a conflict of interest committee to create a management plan, which could "restrict the researcher [from] recruiting subjects; obtaining informed consent; assessing clinical endpoints; analyzing data; or writing the results, conclusions and abstracts for publications reporting the results of the study."
Seton Hall University's Center for Health & Pharmaceutical Law & Policy's 2009 White Paper on conflicts of interest also strongly recommends that conflicts be generally banned. It stresses the need for financial neutrality in clinical trials, especially where physicians and investigators are concerned.\textsuperscript{150} This financial neutrality should be achieved primarily through regulation, since prosecutors generally focus on outlier cases.\textsuperscript{151} The White Paper reviewed common forms of compensation, including when a researcher holds equity in a sponsor, which would give investigators a financial stake in the outcome of the trial.\textsuperscript{152} Such interests should be "prohibit[ed] [as a] form of payment to physicians and other researchers, those in positions to affect the conduct of the research, or to entities conducting the research."\textsuperscript{153} But the White Paper would allow equity holdings by investigators or direct family if the "research could not be conducted effectively or safely without the individual's participation."\textsuperscript{154} In such a "compelling" instance, the investigators role would be limited to that of a consultant, \textit{not} investigator, with no connection to recruitment, enrollment, or informed consent.\textsuperscript{155}

By these restrictive yardsticks, Penn's management of Wilson's conflict stacks up pretty well. Penn told Wilson that "[y]ou are allowed to participate in the design of such studies but shall not be responsible for the analysis of data resulting from such studies."\textsuperscript{156} It established an Oversight Committee to which Wilson had to provide information annually. Penn "tried to manage [concerns about Wilson's role] by precluding [him] from interacting with the subjects or participating in their management, based on the concern that [he] discovered some of the technology and therefore was invested in its success."\textsuperscript{157} Thus, under both the IOM approach and Seton Hall's White Paper approach, Wilson's deal likely would have gone forward. Query whether Wilson would have violated the IOM or White Paper restrictions by revising the trial's protocol or the content of the Consent Form, as long as he did not directly contact a subject or otherwise participate in the management of subjects. Put another way, recommendations to sharply curb financial conflicts likely will not operate on the ground to bar many proposed deals, even those with gargantuan stakes like the ones held by Wilson.

\textsuperscript{150} Kathleen M. Boozang et al., \textit{The Ctr. for Health & Pharm. Law & Policy, Seton Hall Law Sch., Conflicts of Interest in Clinical Trial Recruitment and Enrollment: A Call for Increased Oversight} 1 (2009) [hereinafter "White Paper"].
\textsuperscript{151} \textit{Id.}
\textsuperscript{152} \textit{Id.} at 28.
\textsuperscript{153} \textit{Id.}
\textsuperscript{154} \textit{Id.} at 29. This is consistent with the approach taken by most research universities, 81% of which allow researchers with "significant financial interests" to participate in human research in compelling circumstances. \textit{See} Susan Ehringhaus & David Korn, U.S. Medical School Policies on Individual Financial Conflicts of Interest: Results of an AAMC Survey, \textit{Ass'n of Am. Med. C.} 4 (Sept. 2004), available at http://www.aamc.org/research/coi/coiresults2003.pdf.
\textsuperscript{155} \textit{White Paper, supra} note 150, at 29.
\textsuperscript{156} Letter from Cooperman to Wilson, \textit{supra} note 74.
\textsuperscript{157} \textit{Lessons Learned, supra} note 9, at 156.
VII. AGGRESSIVE MONITORING AS THE WAY FORWARD

A number of research institutions over the last decade have instituted a new regulatory regime that works in conjunction with the IRB process: post-approval monitoring. The goals of post-approval monitoring are straightforward, to “ensure the rights and well-being of research subjects,” as well as “ensur[ing] compliance with federal, state, local, and institutional . . . guidelines.” Rather than seeking to expunge financial ties or police them through disclosure and publication rules, one promising approach may be to marry the IRB and conflict of interest approval processes with medicine’s invigorated culture of regulatory compliance. Under this scheme, any significant financial interest would trigger mandatory, periodic, unannounced audits of the trial’s conduct.

Theoretically, all human trials have been subject to ongoing review by the IRB since the creation of IRBs. In practice, however, the trials watched most closely by institutions that have existing programs for post-approval monitoring tend to be studies that pose moderate to high risk to subjects, investigator-initiated studies, and, most relevant here, studies with possible conflicts of interest. In the post-approval monitoring process, if a study is selected for review, the monitor notifies the principal investigator and reviews the trial’s records. That review may cover any communication with the IRB and other oversight committees, contact with federal regulatory authorities, consent forms and the consent process for individual subjects, whether protocols were adhered to or changed, and whether there were serious adverse events.

While Jesse’s trial may well have been randomly selected for review at institutions that now conduct post-approval monitoring, it would have been

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158 Institutions with post-approval monitoring programs include the University of Virginia, http://www.virginia.edu/vpr/pam/index.html; University of Cincinnati, http://researchcompliance.uc.edu/PAM/Default.html; University of California-Davis, http://safetyservices.ucdavis.edu/iauc/policies/post-approval-monitoring-program; Georgia State University, http://www.gsu.edu/research/22242.html; East Tennessee State University, http://www.etsu.edu/ucac/monitoring.aspx; and University of Mississippi, https://secure4.olemiss.edu/umpolicyopen ((follow “Table of Contents” hyperlink; then follow “RSP Research and Sponsored Programs” hyperlink; then follow “RI Research Integrity” hyperlink; then follow “301 Institutional Review Board” hyperlink; then follow “RSP.RI.301.020 IRB Post Approval Monitoring Program hyperlink) (all last visited April 26, 2010).


160 Professor Jesse Goldner has also urged institutional reforms to conflict of interest committees, such as regulating membership criteria and mandating inclusion of committee members with no institutional connections. Goldner, supra note 147, at 1247. Additionally, “all financial conflicts of interest of any amount” would be disclosed to the conflict of interest committee as well as on a NIH-sponsored website and in the trial’s consent form. Id. at 1248.

161 Conflict of interest committees should describe conflicts of interest in the same section of the informed consent document as the “description of any reasonably foreseeable risks or discomforts to the subject.” Id. at 1249-50 (quoting 45 C.F.R. § 46.116(a)(2)).


163 For an example, see Post Approval Monitoring FAQ, University of Virginia, available at http://www.virginia.edu/vpr/pam/faq.html (last visited April 26, 2010).
purely a matter of chance. Thus, even trials with large financial conflicts of interest may never be monitored despite the possible risk to subjects. While the random nature of any monitoring serves to ensure institutional compliance generally, it would not guarantee that a trial to which a researcher has a significant financial tie would be selected for monitoring.

A mandatory trigger for post-approval monitoring of any trial marked by significant financial conflicts of interest would ensure review of the affected researcher's judgment. In Jesse's case, such a review may have picked up "real-time" changes to the protocol never approved by the IRB. It almost certainly would have uncovered changes to the Consent Form that likely would have discouraged Jesse, if not other participants, from enrolling – namely, the death of monkeys and mice in earlier trials. Mandatory monitoring may have also surfaced other errors, like the adverse events experienced by earlier subjects. The only mistake acknowledged by Wilson that clearly would not have been picked up by mandatory monitoring would have been the decision to infuse Jesse on the day of the trial because no mandatory monitoring could feasibly encompass real-time assessment.

In this mandatory scheme, the threshold for a significant financial interest could be defined institution by institution or by federal regulation. To avoid over-inclusion, the threshold for mandatory monitoring should probably exceed the $10,000 threshold that defines a significant financial interest now under current law. On the equity side, the percentage defined as a significant financial interest may need to take into account the probable market value of the shares now and after a public offering.

In practice, the two institutional entities charged with policing human research and financial conflicts, the IRB and the institution's conflict

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163 Of course, had Wilson been required to divest his shares in Genovo, or if Penn had chosen to run the SRA between Biogen and Penn, decisions in Jesse's trial may have nonetheless unfolded precisely as they did. Obviously in the absence of a conflict, the reform urged here would not have flagged Jesse's trial for special vigilance. Institutions nonetheless could choose to police the possibility of errors in non-conflicted trials through random post-approval monitoring or other mechanisms used by the institution to ensure regulatory compliance.

164 See supra notes 24-25, 43-47 (discussion between Paul and Jesse about the risk of death).

165 Weinfurt et al., supra note 127, at 862, 864 (reporting that many subjects would enroll notwithstanding certain financial ties). In a study of cancer patients receiving experimental treatment, 80% expressed no concern "that the doctor running their study might have financial ties with the company that makes the drug used in the study." Hampson et al., supra note 139, at 2332. "Less than 15% of patients reported that knowledge of a financial tie would have kept them from participating in the cancer trial." Id. Contrasting that statistic with the 13 to 34% of patients who felt that financial ties should be barred led the authors to suspect "that for seriously ill patients, disclosure [of financial ties] is unlikely to provide protection against the potential harm of financial interests." Id. at 2336. Obviously, the risk-benefit calculation of patients in need of experimental therapy for an underlying disease may not predict the assessments that would be made by relatively healthy, functioning participants like Jesse.

166 Nelson & Weiss, supra note 30, at 2 (showing that four successive volunteers suffered side effects so serious that Penn should have halted the study and notified the FDA immediately in every case - but didn't do so for the third or fourth participants).

167 It may be difficult to predict what a market value might be but a probable range could be provided.
committee, may have to work together to monitor studies. The IRB will need to make sure that studies with a potential for high risk to human subjects are monitored on a regular basis, using financial ties as a trigger. In partnership with the IRB, the institution’s conflict of interest committee may need to flag certain studies that exceed pre-established financial thresholds for referral to the IRB. Clearly, these committees would need to coordinate their efforts.

While mandatory monitoring will provide a more effective review process, there undoubtedly will be a substantial cost attached to this increased vigilance. These costs should be considered a “loading charge” for undertaking studies with substantial financial conflicts of interest. Indeed, the cost of monitoring likely will pale in comparison to the financial infusion provided by the SRA. For example, under the terms of Penn’s SRA with Genovo, Genovo provided $21 million for research over 5 years. Even if $100,000 of that sum were allocated to mandatory monitoring, this represents less than half of 1 percent of the sums garnered by Penn as a result of Genovo’s sponsorship.

Not every financial conflict will be on the scale of Wilson’s, and neither will every sponsored research agreement provide for such a substantial infusion of funds. Admittedly, an adequate monitoring program that encompasses smaller but still significant financial ties may be an expensive endeavor if done right—likely requiring several well-trained and knowledgeable full-time staff to cover a busy research institution. Yet institutions like Penn have learned the hard way that review of a research study prior to its implementation does not fully protect human subjects. Post-approval monitoring offers a more meaningful way for institutions to assure that what the investigator says he is going to do is what is actually done. Spending tens or even hundreds of thousands of dollars a year to fund a robust post-approval monitoring program would seem preferable not only to the tragic death of a 19-year-old, but also to the horrendous publicity, expense, and time spent managing the aftermath of profound, yet often preventable, errors in human trials.

Some may see such monitoring as yet another example of paper compliance, with its increasing cost for human subjects research. The cost of monitoring should be the entry fee for engaging in trials with substantial financial ties. Investigators and researchers should not be permitted to explain after a participant’s death, as Wilson did in the Lessons Learned, that 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.\(^\text{169}\)

\(^{169}\) Nelson & Weiss, supra note 17.

\(^{169}\) Lessons Learned, supra note 9, at 154.
As Wilson himself acknowledges, the three investigators in Jesse's trial had pre-existing duties to ensure participant safety separate and apart from efforts to "manage" Wilson's financial conflict. Mandatory post-approval monitoring would make routine the oversight already required by federal regulators, and prevent trials from being undertaken in the haphazard way that marked Jesse's clinical trial.

A more sophisticated critique may say that the whole enterprise of post-approval monitoring is subject to hindsight bias as a result of which, in retrospect and upon further analysis, "[p]ast events seem more predictable than they really were." This bias has been shown in studies of college undergraduates, experts in varied fields, and "even state and federal judges." Like most disasters, Jesse's death was preceded by a number of mistakes. While it is true that hindsight is 20/20, and that we often realize that mistakes were important only after an event, in Jesse's case the mistakes preceding his death were obvious and blatant. Clear and material departures from the protocol, which Wilson himself described as a "living document," unapproved changes to the Consent Form, and records showing "four successive volunteers had suffered side effects so serious that Penn should have halted the study and notified the federal agency immediately in every case -- but didn't do so for the third or fourth patients," certainly would have leapt out to any person charged with monitoring the conduct of Jesse's trial—especially in light of the colossal stakes held by one of the researchers.

VIII. CONCLUSION

Jesse's death sparked a re-examination of researchers' financial ties to the human trials they conduct, an important legacy in itself. Internal Penn documents priced Wilson's financial stake in Jesse's trial to be in the tens of millions of dollars—ample motivation for anyone to cut corners or push research more quickly than it should proceed. Recognizing that potential, Penn's conflict of interest committee honed in on Wilson's precise role in funded trials. Yet when Penn as an institution authorized Wilson's hefty stake, it required that Wilson not "direct[ly] participat[e] in the conduct of clinical trials," leaving him free to make key design decisions. More importantly, Penn simply trusted that these ground rules would be followed. Sadly, the decisions ultimately made in Jesse's trial by Wilson and his colleagues provide powerful testimony to the need for more vigilance. Unlike both the movement to ban financial conflicts and the movement to ratify them, mandatory post-approval monitoring in trials with significant financial conflicts would allow crucial research to be done without neglecting the risk to human subjects that often results. Financial triggers for mandatory review would be a significant step in protecting future human subjects who, like Jesse Gelsinger, deserve our continued vigilance and commitment.

171 Id. at 579–80.
172 Lessons Learned, supra note 9, at 155.
173 Nelson & Weiss, supra note 30, at 3.