Conflict of Interest

11

Arthur L. Caplan and Barbara K. Redman

Conflict of interest (COI) describes a situation in which the impartiality of research may be compromised by the researcher standing to profit in some way from conclusions drawn in the research. This can be a conflict among roles as when a researcher takes on too many outside consulting duties and neglects mentoring students, or misses classroom teaching, or a conflict of trust when the ability to make money from offering a particular interpretation of findings distorts trust in the analysis or conclusions reached. COI can occur at individual, institutional, or industry level or in a particular case, at several of these levels at once. Conflicts can arise from financial, ideological, political, religious beliefs, or personal relationships. Transparency through the disclosure of financial COIs has been the main management technique for handling COI. But it is suboptimal because it provides no way to know for sure whether competing interests have compromised the research (Dunn et al. 2016). There is no detailed federal policy in the USA on identifying or managing institutional conflicts of interest. A survey by Resnik (2016) found that only 38% of top grant getting institutions had such policies.

Cases in this chapter and in the suggested supplementary readings provide examples of COI and how they might be handled. Historical evidence of an NIH institute being captured by the sugar industry while setting its research priorities yielded unfortunate results for controlling disease. Tactics were similar to those used by tobacco, lead, and other industries – using funding to divert the research agenda to protect their products (Kearns et al. 2015). In the case of the death of Jesse Gelsinger in a gene therapy trial at the University of Pennsylvania, both individual and institutional conflicts of interest involving patents for vector technology were present. The principal investigator of that trial in various subsequent writings identified lessons learned, which included more rigorous restrictions to separate the investigator and physician caretaker roles and limitation of trial involvement by an investigator with a stake in a company whose value could be affected by the outcome of the trial (Wilson 2009). Elliott (2016) describes a complex web of conflicts by a university in its oversight role in the protection of human subjects. Review of this situation by an independent external group provided insights into best practices for minimizing conflicts including a greater role for those not affiliated with the institution on review committees.

Potential COIs can be found in many areas of research production, dissemination and oversight. Campbell et al. (2015) found industry COI on the part of 30% of IRB members and noted that 25% of conflicted members voted on a protocol on which they were conflicted, which is an ethical violation—they should have recused themselves. At the same time, since discussion of the commercial purpose of a study and researcher compensation are not part of IRB review, members cannot discuss how interests of the researcher may conflict with interests of the research subject (participant). Meta-analyses (MA) of antidepressant trials found 30% of authors to be employees of the drug manufacturer with a total of 79% of authors having industry links. Those with employee authors were much less likely than were other studies to have negative statements about the drug.

COIs do not automatically invalidate scientific work but rather raise a question about whether a scientist or institution

A. L. Caplan · B. K. Redman (✉)
New York University Langone Medical Center,
New York, NY, USA
e-mail: Arthur.Caplan@nyumc.org

A. L. Caplan, B. K. Redman (eds.), *Getting to Good*, https://doi.org/10.1007/978-3-319-51358-4_11

has been careful in their role and impartial. Some COIs could be seen as inherent in certain structures (IRB action on proposals that bring money to the university that appoints IRB members) but may be counterbalanced with benefits from this arrangement such as local knowledge of the trustworthiness of investigators.

Advice: Know how to identify potential COIs, how to evaluate evidence when they are present. Seek to minimize COI by not undertaking outside work that greatly interferes with your primary duties and never accepting support that is contingent on reaching a particular conclusion in your work. If you are evaluating your own work prior to publishing or that of others, do not be the only one to do so if you have COI. Always disclose any concerns you have about possible COI to editors, regulatory bodies, and colleagues.

11.1 Sugar Industry Influence on the Scientific Agenda of the National Institute of Dental Research's 1971 National Caries Program: A Historical Analysis of Internal Documents

Cristin E. Kearns, Stanton A. Glantz, and Laura A. Schmidt

Kearns, C, Glantz, S, Schmidt, L. Sugar industry influence on the scientific agenda of the National Institute of Dental Research's 1971 National Caries Program: A historical analysis of internal documents. *PLoS Medicine* 12(3), e1001798 (2015).

PLOS | MEDICINE

RESEARCH ARTICLE

Sugar Industry Influence on the Scientific Agenda of the National Institute of Dental Research's 1971 National Caries Program: A Historical Analysis of Internal Documents

Cristin E. Kearns[1,2,3], **Stanton A. Glantz**[1,2,4,5]*, **Laura A. Schmidt**[1,2,6,7]

1 Philip R. Lee Institute for Health Policy Studies, University of California San Francisco, San Francisco, California, United States of America, **2** Department of Medicine, University of California San Francisco, San Francisco, California, United States of America, **3** Department of Orofacial Sciences, University of California San Francisco, San Francisco, California, United States of America, **4** Center for Tobacco Control Research and Education, University of California San Francisco, San Francisco, California, United States of America, **5** Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, California, United States of America, **6** Clinical and Translational Science Institute, University of California San Francisco, San Francisco, California, United States of America, **7** Department of Anthropology, History and Social Medicine, University of California San Francisco, San Francisco, California, United States of America

* glantz@medicine.ucsf.edu

Citation: Kearns CE, Glantz SA, Schmidt LA (2015) Sugar Industry Influence on the Scientific Agenda of the National Institute of Dental Research's 1971 National Caries Program: A Historical Analysis of Internal Documents. PLoS Med 12(3): e1001798. doi:10.1371/journal.pmed.1001798

Academic Editor: Simon Capewell, University of Liverpool, UNITED KINGDOM

Received: October 30, 2014

Accepted: January 29, 2015

Published: March 10, 2015

Data Availability Statement: The Roger Adams Papers, 1812–1971, Record Series Number: 15/5/23 are available for research at the University of Illinois Archives at 19 Library, 1408 W. Gregory Drive, Urbana, IL 61801.

Funding: This work was supported by the UCSF Philip R. Lee Institute for Health Policy Studies, a donation by the Hellmann Family Fund to the UCSF Center for Tobacco Control Research and Education, the UCSF School of Dentistry Department of Orofacial Sciences and Global Oral Health Program, National Institute of Dental and Craniofacial Research

Abstract

Background

In 1966, the National Institute of Dental Research (NIDR) began planning a targeted research program to identify interventions for widespread application to eradicate dental caries (tooth decay) within a decade. In 1971, the NIDR launched the National Caries Program (NCP). The objective of this paper is to explore the sugar industry's interaction with the NIDR to alter the research priorities of the NIDR NCP.

Methods and Findings

We used internal cane and beet sugar industry documents from 1959 to 1971 to analyze industry actions related to setting research priorities for the NCP. The sugar industry could not deny the role of sucrose in dental caries given the scientific evidence. They therefore adopted a strategy to deflect attention to public health interventions that would reduce the harms of sugar consumption rather than restricting intake. Industry tactics included the following: funding research in collaboration with allied food industries on enzymes to break up dental plaque and a vaccine against tooth decay with questionable potential for widespread application, cultivation of relationships with the NIDR leadership, consulting of members on an NIDR expert panel, and submission of a report to the NIDR that became the foundation of the first request for proposals issued for the NCP. Seventy-eight percent of the sugar industry submission was incorporated into the NIDR's call for research applications. Research that could have been harmful to sugar industry interests was omitted from priorities

PLOS | MEDICINE

grant DE-007306 and National Cancer Institute Grant CA-087472. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Abbreviations: FAO, Food and Agriculture Organization; FDA, Food and Drug Administration; ISRF, International Sugar Research Foundation; NCI, National Cancer Institute; NCP, National Caries Program; NIDR, National Institute of Dental Research; NIDCR, National Institute of Dental and Craniofacial Research; NIH, National Institutes of Health; RFC, request for contracts; SA, the Sugar Association; SRF, Sugar Research Foundation; TIRC, Tobacco Industry Research Committee; TWG, Tobacco Working Group; WHO, World Health Organization; WSRO, World Sugar Research Organisation.

identified at the launch of the NCP. Limitations are that this analysis relies on one source of sugar industry documents and that we could not interview key actors.

Conclusions

The NCP was a missed opportunity to develop a scientific understanding of how to restrict sugar consumption to prevent tooth decay. A key factor was the alignment of research agendas between the NIDR and the sugar industry. This historical example illustrates how industry protects itself from potentially damaging research, which can inform policy makers today. Industry opposition to current policy proposals—including a World Health Organization guideline on sugars proposed in 2014 and changes to the nutrition facts panel on packaged food in the US proposed in 2014 by the US Food and Drug Administration—should be carefully scrutinized to ensure that industry interests do not supersede public health goals.

Introduction

Despite overwhelming consensus on the causal role of sugars in tooth decay [1] and recommendations by expert committees [2–4], quantitative targets restricting the intake of sugars to control dental caries have not been widely implemented [5]. In 2003, a joint committee of the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) recommended limiting "free" or added sugars, defined as "monosaccharides and disaccharides added to foods by the manufacturer, cook or consumer, and sugars naturally present in honey, syrups, fruit juices and fruit concentrates" to 10% of total calories [3]. The World Sugar Research Organisation (WSRO), a trade organization representing more than 30 international members with economic interests in the cane and beet sugar industry, including the Sugar Association (SA) in the US and Coca-Cola [6], successfully blocked the 2003 WHO/FAO joint committee recommendation from becoming WHO policy [7]. The WHO/FAO joint committee quantitative recommendation to limit free sugars [3] was replaced with the nonspecific recommendation to "limit the intake of free sugars" [8]. In 2014, based largely on the global burden of dental disease, the WHO Nutrition Guidance Expert Advisory Group issued draft guidelines with strong quantitative recommendations to limit daily consumption of free sugars to 10% of total calories, with a further suggestion to limit free sugars to less than 5% of total calories [4]. As with the 2003 WHO recommendation, WSRO and its members have submitted comments in opposition to the 2014 WHO draft recommendation [9,10] and have signaled willingness to contest the 2014 recommendations with equal force as in 2003 [11,12]. WSRO argued that dental public health interventions should focus on reducing the harm of sugar consumption with methods such as the "regular use of fluoride toothpaste" rather than restricting sugar intake [9,13].

Publications about food industry influence on public health policy are growing [14–21], but analyses of food industry documents are rare [22]. Historical analyses of internal tobacco industry documents have proven key to informing policy and litigation successes in tobacco control [23–27]. There are similar historical internal documents related to WSRO that could inform public health efforts by illuminating sugar industry activities designed to undermine or subvert policies to restrict sugar consumption [28].

We analyzed previously unexplored sugar industry documents to trace industry interactions with the US National Institute of Dental Research (NIDR, which changed its name to the

National Institute of Dental and Craniofacial Research [NIDCR] in 1998) between 1966 and 1971, a critical period for dental caries control policy when the NIDR planned the launch of the National Caries Program (NCP) with the goal of eradicating dental caries within one decade [29]. Reflecting the research priorities of the sugar industry, the 1971 NCP research priorities ignored strategies to limit sugar consumption and focused instead on fluoride delivery, reducing the virulence of oral bacteria, and modifying food products with additives to counter sugar's harmful effects [30]. Ultimately, the NCP, which drove the US dental caries research agenda for more than a decade, failed to significantly reduce the burden of dental caries [31], a preventable disease that remains the leading chronic disease in children and adolescents in the US [32].

Methods

Data Sources

Sugar industry documents. This study drew substantially on previously unexplored WSRO-related internal documents from between 1959 and 1971 [33]. WSRO was formed from a number of related sugar industry trade organizations including the Sugar Research Foundation (SRF) and the International Sugar Research Foundation (ISRF) (Fig. 1) [6,34–36]. The first author located these documents in 2010 in an inventory of the papers of Roger Adams housed in the University of Illinois Archives through a Google search using the terms "International Sugar Research Foundation" and "archives" [33]. Roger Adams, Emeritus Professor of Organic Chemistry, served on the SRF and then ISRF Scientific Advisory Board [37] from 1959 until his death in 1971 [38,39]. Adams's files contain correspondence with sugar industry executives, meeting minutes, and other relevant reports. After reviewing the inventory

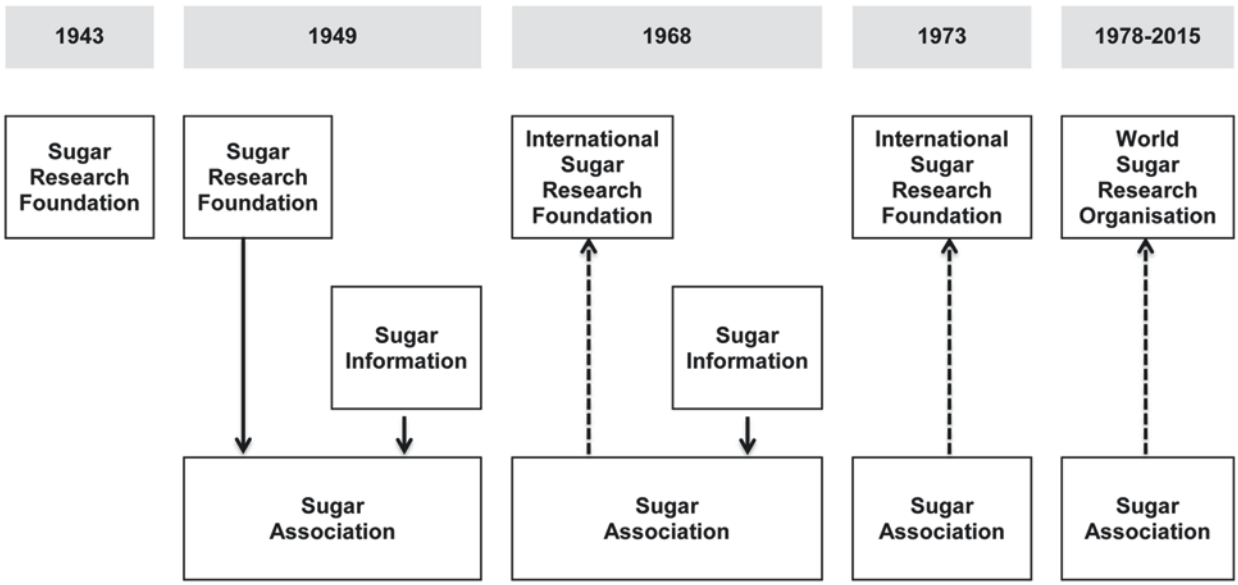

Fig 1. Two sugar industry organizations operating as of 2015, the World Sugar Research Organisation and the Sugar Association, evolved out of the Sugar Research Foundation. In 1943, SRF was founded in New York, New York. In 1949, SA was created to oversee the research activities of SRF (the research arm) and the newly created Sugar Information (the public relations arm). In 1968, SRF dissociated from SA and was reorganized as ISRF. SA joined ISRF as a member (shown as a dotted line). In 1973, SA discontinued Sugar Information because there was no longer a meaningful separation of duties between SA and Sugar Information. In 1978, ISRF was reorganized to become WSRO, and SA joined WSRO as a member.

doi:10.1371/journal.pmed.1001798.g001

of the Roger Adams papers and consulting with University of Illinois archivists, the first author identified 319 documents (1,551 pages) related to SRF/ISRF. Additional material authored by SRF, ISRF, and WSRO was located through a WorldCat search, including annual reports, symposium proceedings, and reviews of research. Documents were carefully reviewed for relevance to dental caries research and policy.

National Institute of Dental Research documents. We located sources related to the NIDR NCP through searches of PubMed and WorldCat, and by contacting NIDCR directly. Materials included NCP primary publications [40–45] and two historical reviews commissioned by the NIDR: a description of the first decade of the NCP by its project officer, William E. Rogers [29], and a history of the NIDR by historian Ruth Roy Harris [31].

Findings were assembled chronologically into a narrative case study. Part of the analysis called for systematically comparing two key reports for similarities: (1) *Dental Caries Research—1969* [46], a document submitted by ISRF to the NIDR, and (2) the NIDR's 1971 *Opportunities for Participation in the National Caries Program* [30], which defined the research priorities at the launch of the NCP. Both documents were entered into Microsoft Word using a monospaced font at 12 characters per inch (average of 12 words per line). After line numbering both documents, we compared the documents, classifying each line of the 1971 NIDR document and the 1969 ISRF document as different, paraphrased, or verbatim. "Paraphrased" was defined as some identical words with the same overall meaning.

Results

Emergence of the National Caries Program, 1966–1967

Table 1 provides a timeline of events during the planning and launch of the NCP.

In June 1966, President Lyndon Johnson initiated a major reappraisal of National Institutes of Health (NIH) research agendas, requesting that directors of NIH institutes submit their programs' "priorities and objectives in the national attack on disease and disability" [29]. The NIDR Director Seymour Kreshover's report to President Johnson in November 1966 stated that "an accelerated program of research during the next decade could reasonably provide the means for virtual eradication of dental caries" [31].

The threat of the NIDR's dental research program to the sugar industry began to crystallize in July 1967, after the president praised Kreshover's report [31]. While it had long been known that bacteria caused tooth decay [54], Kreshover based his plans on the work of NIDR scientists Robert Fitzgerald and Paul Keyes, who had singled out the bacterial strain *Streptococcus mutans* as a major culprit in the production of acids that caused dental caries [55,56]. Research suggested that sucrose was more hazardous than other types of sugars because it caused *S. mutans* to form dextrans, sticky molecules that caused the bacteria to tenaciously adhere to one another in the plaque and on the tooth's surface [57]. The NIDR's increased interest in *S. mutans* brought renewed scrutiny to sucrose consumption and dental caries risk.

In October 1967, the NIDR's National Dental Advisory Council identified three main areas of emphasis to inform research priorities to eradicate caries: reducing the virulence of bacteria once exposed to sugars, fluoride delivery, and, of most concern to the sugar industry, dietary modification [31]. A particular threat was research conducted by NIDR scientist Robert Stephan, initiated in the 1940s, on the "cariogenic" (decay-causing) potential of foods [58–60]. According to Stephan, as of 1966:

> There have been a great many observations, discussions, and controversies published in the literature concerning the role of different foods and particularly sweets in the etiology [of

Table 1. Timeline of events of sugar industry influence on the scientific agenda of the National Institute of Dental Research's 1971 National Caries Program.

Key Dates	NIDR	SRF and ISRF
1959		Roger Adams becomes member of SRF Scientific Advisory Board [37]
June 1966	NIDR Director Seymour Kreshover initiates planning for what would become NCP [29,31]	
1967		SRF funds Project 269 to develop dextranase enzyme and vaccine [47]
June 1968	Announcement of Caries Task Force [31]	Philip Ross (with ties to the US National Institutes of Health) elected ISRF president [48,49], coordinates meetings with the NIDR prior to NCP launch [50]
June 1969		Symposium on the Status of Research in Sucrochemistry, Diet and Heart Disease, Obesity, Dental Caries, and Clinical Nutrition held; Prof. G. Neil Jenkins speaks on "Sugar and Dental Caries" [51]
Sept. 1969		Symposium held: Seeking New Approaches to Old Problems; the NIDR's Richard Greulich speaks on "The Future of Caries Control" [52]
Oct. 1969	Caries Task Force Steering Committee meeting on research priorities; planning for Role of Human Foodstuffs in Caries Workshop Conference [29]	ISRF convenes Panel Meeting of the Dental Caries Task Force—members of the NIDR Caries Task Force Steering Committee participate [53]
Late 1969		Submission of ISRF report *Dental Caries Research—1969* to the NIDR Caries Task Force [46]
Jan. 1970	NIDR Laboratory of Microbiology chief Henry Scherp submits *A National Caries Program of the National Institute of Dental Research: Ten-Year Program of Research and Development*; Nixon selects NCP as special health initiative to be funded in fiscal year 1971 [41]	
Feb. 1970	President Nixon endorses NCP [31]	Celebratory *International Sugar Research Foundation Special Report: Dental Caries* mailed to Roger Adams [50]
March 1970	Caries Task Force holds Role of Human Foodstuffs in Caries Workshop Conference [42]	
March 1971	NCP becomes operational [29]; Omnibus request for contracts, *Opportunities for Participation in the National Caries Program*, released [30]	

doi:10.1371/journal.pmed.1001798.t001

> dental caries]. However. . .there seems to be little controlled experimental proof to show which foods are cariogenic and which noncariogenic in humans. [61]

Stephan had initiated work to develop an animal model that could "evaluate cariogenicity and anticariogenicity of different foods and beverages that people like and commonly consume" [61]. Based on existing research at the time, foods containing sucrose were in danger of being placed at the top of the list of harmful cariogenic products [62].

Industry Deflection of Attention Away from Limiting Sugar Intake

Industry position on caries control. At least as early as 1950, SRF knew its product damaged teeth and appreciated that both the scientific evidence and the dental community favored restricting sugar intake as a key way to control caries [63]. The 1950 SRF annual report stated:

> The ultimate aim of the Foundation in dental research has been to discover effective means of controlling tooth decay *by methods other than restricting carbohydrate intake*. This program has both laboratory and clinical aspects.
>
> *There is evidence tending to show that carbohydrates, including sugar, and perhaps other food types, are implicated in tooth decay*. There is also evidence, though less convincing, that soluble sugars may play a bigger role than starches. Besides the relatively clear evidence there are many conjectures, traditions and myths that confuse the picture.
>
> *Until recently the great majority of the dental profession had adopted the view that practical control of tooth decay could be achieved only by restriction of carbohydrates, particularly sugar in the diet*. Scientific logic, nevertheless, points to many other promising possibilities and many of these are supported by preliminary laboratory observations. [63] (emphasis added)

The 1950 SRF annual report also shows that industry research was selected as part of a strategy to deflect attention away from sugar restriction as a means to control caries [63].

Funding research to divert attention from limiting sugar intake. Consistent with a deflection strategy, between 1967 and 1970, SRF funded Project 269 to bolster research on interventions not requiring sugar restriction to control dental caries [47]. Project 269, led by Professor Bertram Cohen at the Royal College of Surgeons of England, sought to render *S. mutans* less destructive to teeth after sugar was consumed using enzymes called dextranases to break the sticky dextrans in dental plaque formed after sugar was consumed [47]. Project 269 also attempted to develop a vaccine against tooth decay that would allow people to continue to consume sugar [47]. The NIDR had investigated both methods in the 1960s [31] and found that although dextranases added to the food and water of rodents had shown some promise of being effective, more research was necessary before human applications could be developed [64], and a vaccine against *S. mutans* tested in hamsters failed to prevent tooth decay [65]. By 1962, NIDR scientists were suggesting that measures other than a vaccine would be needed to control dental caries [31].

SRF allocated US$12,000 (US$85,455 in 2014 dollars) to Project 269 between 1967 and 1970 [47]. Project 269 was primarily funded by the chocolate and confectionary industries and had an annual budget of US$120,000 (US$854,558 in 2014 dollars) [47]. A confidential report mailed to Roger Adams summarizing Project 269 indicated that SRF considered dental caries "one of the major troublesome factors in the nonacceptance of sucrose" [47]. SRF leaders hoped that their support for this new project would prove a "significant way of solving the problem" [47].

Funding from SRF and the chocolate and confectionary industry allowed Cohen to create a new laboratory to use monkeys for the development of dextranases and a tooth decay vaccine for human application [47]. SRF hoped that the work on dextranases and a vaccine could be handed over to drug companies to develop commercial quantities [47]. A 1968 *Montreal Gazette* article, "These Monkeys May Save Your Teeth," reported that one practical application for dextranase under consideration was "to mix it with raw sugar and use it as a powder on

desserts and cakes and in soft drinks" [66]. Cohen was described as having "little sympathy for those who would ban sweet things," and was quoted as saying "Why should people be denied pleasure? It would obviously be far better to eliminate the harmful effects" [66]. While at the time there was less attention paid to scientific conflicts of interest than in 2015, the article mentioned that a grant from the Nuffield Foundation funded the building of the research unit that housed the monkeys, but not that the sugar or chocolate and confectionary industries were also supporting Cohen's work [66].

Setting Research Priorities for the National Caries Program, 1968–1969

At a June 1968 press conference, NIDR Director Kreshover announced the creation of the Caries Task Force chaired by NIDR Laboratory of Microbiology chief Henry Scherp to develop the NCP [31]. A subcommittee, the Caries Task Force Steering Committee, was assigned the essential task of identifying research priorities [29]. Task force members were largely drawn from federal agencies and academia (Table 2). Professor Basil Bibby, with a strong background in developing models that could evaluate the cariogenicity of foods, would be assigned a leading role in evaluating research supporting dietary interventions to eliminate tooth decay [29].

In 1968, SRF reorganized as ISRF to carry on SRF's research mission at the global level [48]. Existing SRF research projects, including Project 269, continued to be supported by ISRF [67]. ISRF was also interested in engaging federal research agencies. On July 1, 1968, Dr. Philip Ross became ISRF president [48]. Ross had ties to the NIH, having served as chief of the NIDR/NIH Research Grants Section from 1963 to 1965, then as assistant head of the NIH Special International Programs Section until 1967 [49]. Moreover, that summer, ISRF moved its headquarters from New York to Bethesda, Maryland, near the NIH [68].

Industry reviews dental caries literature. As the NIDR Caries Task Force Steering Committee began meeting to discuss research priorities in 1969, ISRF scheduled a series of meetings

Table 2. Comparison of membership of the NIDR Caries Task Force Steering Committee and ISRF Panel Meeting of Dental Caries Task Force.

Name	Affiliation	NIDR Caries Task Force Steering Committee, 1969 [31]	ISRF Panel Meeting of Dental Caries Task Force, October 20, 1969 [53]
Basil G. Bibby	Director, Eastman Dental Center	X	X
George W. Burnett	Professor of Microbiology, School of Dentistry, Medical College of Georgia	X	X
James P. Carlos	Chief, Biometry Section, NIDR		X
Charles J. Donnelly	Chief, Dental Caries and Hard Tissues Program, Extramural Programs, NIDR	X	X
Robert J. Fitzgerald	Laboratory of Microbiology, NIDR	X	
John C. Greene	Deputy Director, Division of Dental Health, Bureau of Health Professions, Education of Manpower Training, NIH	X	X
Robert S. Harris	Professor of Nutritional Biochemistry, Massachusetts Institute of Technology	X	X
John Knutson	Professor of Preventive Dentistry, School of Dentistry, University of California, Los Angeles	X	X
Bo Krasse	Professor of Cariology and Dean, Faculty of Odontology, University of Gothenburg, Sweden		X
Seymour Kreshover	Director, NIDR and Caries Task Force Steering Committee	X	X
Henry W. Scherp	Chief, Laboratory of Microbiology, NIDR, Chairman Caries Task Force	X	X

doi:10.1371/journal.pmed.1001798.t002

Table 3. Comparison of Research Priorities Identified by ISRF and the NIDR, 1969–1971.

Feasible Interventions to Eradicate Dental Caries	(A) Prof. G. Neil Jenkins address to ISRF, "Sugar and Dental Caries," June 1969 [51]	(B) NIDR's Richard Greulich address to ISRF, "The Future of Caries Control," September 1969 [52]	(C) NIDR Caries Task Force Steering Committee, October 1969 [29]	(D) ISRF Panel Meeting of the Dental Caries Task Force, October 1969 [71]	(E) ISRF Submission to the NIDR: *Dental Caries Research—1969*, Late 1969 [46]	(F) NIDR Caries Task Force Role of Human Foodstuffs in Caries Workshop Conference, March 1970 [72]	(G) NIDR Request for Contracts, *Opportunities for Participation in the National Caries Program*, 1971 [30]
Dietary interventions							
Cariogenic potential of foods			Deferred to March 1970 meeting			X	
Dietary phosphates	X	X	X	X	X	X	X
Invert sugars		X	X			X	X
Dietary trace elements	X		X	X		X	X
Non-dietary interventions							
Dextranase	X	X	X	X	X	N/A	X
Low molecular weight dextrans		X	X		X	N/A	X
Antimicrobial agents			X	X	X	N/A	X
Antibiotics			X		X	N/A	X
Immunization	X		X	X	X	N/A	X
Water fluoridation	X		X	X	X	N/A	
Topical application of fluoride	X		X		X	N/A	X
Addition of fluoride to sugar, salt, flour			X	X	X	N/A	
Sealants		X	X	X	X	N/A	X
Other						N/A	
Dental epidemiology			X			N/A	
Education for motivation			X			N/A	

N/A, not applicable.

doi:10.1371/journal.pmed.1001798.t003

to select "the areas of research that [ISRF] should be attacking" [69]. Table 3 provides an overview of the research priorities discussed by the NIDR and ISRF committees at key moments leading up to the launch of the NCP. According to ISRF President Ross, ISRF meetings would consider "critical reviews of the major areas [concerning] sugar," including a range of public health topics: "dental caries, overweight and obesity, [and] atherosclerotic vascular disease" [69]. Panels of outside consultants would be convened, and the results of these activities compiled and sent to ISRF Scientific Advisory Board members by December 1969 [70].

ISRF launched its critical review of dental caries by inviting Dr. G. Neil Jenkins, a professor at the University of Newcastle Dental School, to speak at an ISRF symposium in London in June 1969 [51]. Jenkins's assessment of research on interventions that reduced the harm of sugar consumption without restricting intake (Table 3, column A) was largely unfavorable [51]. Jenkins reviewed food additives, which in preliminary studies reduced the yield of bacterial acid produced after sugar consumption, and concluded that the dose of additives needed might be so high as to render the methods impractical or cause harmful side effects [51]. Perhaps unaware that ISRF was supporting research on dextranase and a tooth decay vaccine at the time under Project 269, Jenkins expressed skepticism about these lines of research:

> Several lines of evidence have tended to emphasize, and perhaps exaggerate, the importance of dextrans.. . .As an enzyme its instability would limit its application, and the whole basis of this idea depends on the unresolved question of the importance of dextrans. [51]

On the caries vaccine Jenkins noted, that while "a successful preliminary experiment along these lines has been reported in three monkeys," the promise of this result was limited because "it is admitted that the organisms used in the above experiment would be unsuitable for human use and it is not yet possible to incriminate any individual species [of bacteria] as the sole cause of human caries" [51]. Jenkins saw fluoridation as "the only thoroughly well-established method of reducing caries which does not require the active (and usually reluctant) participation of the patient" [51].

Industry receives a preview of the NIDR's research priorities. ISRF got a preview of the NIDR's research priorities for the NCP at the second ISRF symposium in September 1969 in Bethesda [52]. Richard Greulich, the NIDR's intramural scientific director [31], spoke on "The Future of Caries Control" one month before the NIDR Caries Task Force Steering Committee would first discuss NCP research priorities (Table 1) [52]. Greulich said that while water fluoridation (which had been accepted in the US in 1965 as a "proved highly beneficial public health measure ready for widespread implementation" [29]) had achieved some success, The NIDR knew it was not the sole answer to eradicating dental caries:

> From a public health point of view, we do not feel confident that fluoride is the only answer; and biologically speaking, it obviously is not because we have not talked to the other enterprises here. We have mentioned a host factor as represented or reflected by fluoridation. We have not talked to the microbes; we have not talked to the substrate or to nutrition. [52]

Greulich's symposium presentation downplayed the value of limiting sucrose consumption as a means to control dental caries:

> One could say, on logical grounds and good evidence, that if we could eliminate the consumption of sucrose, we could eliminate the problem—because we would be denying these pathogens their primary source of nutrient. We are realists, however, and we recognize the value of sucrose to nutrition. So *while it is theoretically possible to take this approach to demonstrate it, and it has been demonstrated certainly in animal models, it is not practical as a public health measure*. It is like saying the maximum speed of a jet plane is the speed of light. It just is not practical to try and evolve on to that point. And so in smooth surface caries, we have a more practical goal in working on the microorganism. [52] (emphasis added)

Similar to the approaches the sugar industry was promoting, Greulich identified interventions targeting bacteria as promising to the NIDR (Table 3, column B), including dextranases, for

which the NIDR had been working with the pharmaceutical company Merck Sharpe & Dohme to think through the steps necessary for practical application [52]. The NIDR was also hopeful about a laboratory finding on "low molecular weight dextrans," another substance that might be delivered to keep bacteria from producing harmful acid when exposed to sugar [52].

Beyond its focus on decay-causing bacteria, Greulich told ISRF that the NIDR was investigating ways to modify sugar to reduce its harmful effects [52]. These dietary modification interventions included adding phosphates to sugar, and the possibility of replacing table sugar, in the form of sucrose, with a liquid sugar, that split the sucrose molecules into glucose and fructose, which were thought to be less harmful to teeth [47]. Just before concluding, Greulich again assured ISRF that the NIDR research was not a threat to sugar consumption: "I reiterate that the role of sucrose [in dental caries] is undeniable, yet there is very little that anyone would want to do about this other than to explore some of these possible [dietary] modifications" [52].

Industry convenes a panel that includes many members of the NIDR Caries Task Force. In October 1969, the NIDR Caries Task Force Steering Committee met to identify research priorities [29]. As Greulich predicted, the main approaches reviewed focused on interfering with bacteria and dietary modification of sugar (Table 3, column C) [29]. However, a summary of the Caries Task Force Steering Committee meeting indicates that they "also reviewed the agenda for a conference on the role of human foodstuffs in dental caries" [29]. Caries Task Force Steering Committee member Basil Bibby would participate in the conference organization [42], and would have the chance to discuss the state of research on models identifying the cariogenicity of foods with the Caries Task Force, but not until March 1970 [43].

In October 1969, the same month the Caries Task Force Steering Committee was evaluating research priorities to eradicate dental caries (Table 1) [31,71], ISRF President Ross convened his Panel Meeting of the Dental Caries Task Force to consult on ISRF's dental caries research priorities [53]. As Table 2 illustrates, the membership of ISRF's panel overlapped almost completely with the NIDR Caries Task Force Steering Committee. All members of the NIDR Caries Task Force Steering Committee sat on the ISRF expert panel, with the exception of Fitzgerald, whose research on *S. mutans* had identified sucrose as the worst offender in smooth surface cavities [31,53]. The significant overlap between the membership of the ISRF expert panel and that of the NIDR Caries Task Force Steering Committee gave ISRF direct access to the NIDR's Caries Task Force Steering Committee.

ISRF's summary of the ISRF Panel Meeting of the Dental Caries Task Force indicates that the ISRF panel "recommended that a study be made of the cariogenicity of carbohydrate-containing foodstuffs" but did not mention studying the tooth-decay-causing potential of foods in its final "major approaches to caries" [71] (Table 3, column D).

Industry submits recommendations to the NIDR. ISRF submitted the findings from its series of meetings to the NIDR Caries Task Force late in 1969 in a report titled *Dental Caries Research—1969* [46]. While recognizing the causative role of sugar in tooth decay, ISRF downplayed the feasibility of restricting consumption of sugars while promoting advances made in areas of dextranase and caries vaccine research [46]. It also summarized dental caries interventions that would reduce the harm of sugar without impacting consumption, including phosphate food additives, protective sealants, and fluoride delivery through expanded community water programs, topical application, and addition to sugar, salt, or flour [46]. The research priorities identified by the NIDR Caries Task Force Steering Committee in October 1969 (Table 3, column C) are strongly aligned with ISRF's submission (Table 3, column E), with the notable exception of developing a model to identify the cariogenicity of foods.

During fall 1969, the Nixon administration focused on biomedical research policy and showed signs of interest in supporting the NCP [31]. In January 1970, Caries Task Force

Chairman Scherp submitted the report *A National Caries Program of the National Institute of Dental Research: Ten-Year Program of Research and Development* [41] in response to a request from the Office of the Secretary of Health, Education, and Welfare for a detailed plan for developing dental caries interventions [31]. Scherp's report was based on the work of the NIDR Caries Task Force Steering Committee at its October meeting [31]. Later that month, the Assistant Secretary for Health indicated that President Nixon would endorse the program [31].

Launch of the National Dental Caries Program, 1970–1971

During his February 1970 budget message, President Nixon announced support for "substantial increases in research on cancer, heart disease, serious childhood illnesses, and dental health—where current findings promise significant advances for the future" [31]. A line item in the budget allocated US$5 million (US$30.6 million in 2014 dollars) for the NCP in fiscal year 1971 [29].

In February 1970, after President Nixon's public endorsement of the NCP but before the NIDR officially released the NCP research priorities, ISRF mailed its report *International Sugar Research Foundation Special Report: Dental Caries* [50] to its Scientific Advisory Board. The ISRF report began, "The correlation between sugar and dental decay—a practical concern of the sugar industry for many years—may become a purely academic issue within the foreseeable future," then described the work ISRF leaders had invested to influence the NCP [50]. ISRF President Ross had collaborated with the NIDR Caries Task Force Chairman Scherp and had submitted a report created by ISRF staff on dental caries research priorities directly to the NIDR Caries Task Force:

> Dental caries has been a constant worry to many consumers of sugar and sugar products. To some scientists, dental caries and sugar are considered almost "synonymous." ISRF, in its concern about this image, has supported research to uncover many of the unknowns, and has kept in close communication with other institutions which concentrate on such research. The National Institute of Dental Research, of the U.S. Public Health Service's National Institutes of Health, is the most prominent U. S. organization conducting dental caries research on a broad scale. Last year the Institute formed a Dental Caries Task Force to work "toward the goal of virtually eliminating tooth decay in the United States." Dr. Philip Ross, ISRF President, met with the Dental Caries Task Force and has worked closely with its Chairman, Dr. Henry W. Scherp. Dental Caries Research—1969, prepared several months ago by the staff of ISRF, reviewed current knowledge of the subject and was submitted to the Task Force for its consideration. [50]

The NIDR Caries Task Force held its conference on dietary research priorities one month later (Table 1) [42]. At the NIDR Role of Human Foodstuffs in Caries Workshop Conference, Caries Task Force Steering Committee member Basil Bibby presented a paper, "Methods for Comparing the Cariogenicity of Foodstuffs," which reviewed the status of research on experimental models to identify food products harmful to teeth [43]. These models were important, according to Bibby, because it was "desirable to have a relatively speedy and economical method of evaluating cariogenicity, especially of snack-type foods, so that parents can be warned against the more destructive products" [43]. Bibby's presentation summarized 12 different models to identify the cariogenicity of foods, ranging from "acid production from foods incubated in saliva" to the production of caries in rats, monkeys, and pigs [43]. During the discussion of Bibby's presentation, Caries Task Force members established that "a quick screening method was needed to provide presumptive evidence of the potential cariogenicity of accepted

foods and new products that appear almost daily on the shelves of food markets," although there were differences of opinion on what the best model would be to screen for cariogenicity [44]. No one argued that the NIDR not pursue standardization of a test that would rank foods on their potential for tooth decay [44].

Comparison of ISRF and the NIDR Research Priorities

Soon after Nixon's February 1970 endorsement of the NCP, Scherp began operational planning for program implementation at the NIDR [29]. Research priorities were first published in an omnibus request for contracts (RFC) [29] titled *Opportunities for Participation in the National Caries Program* [30] in early 1971. The NIDR received 112 proposals and funded 17 contracts [29] totaling US$3 million (US$18.3 million in 2014 dollars) out of the NCP's budget of US$6 million (US$36.7 million in 2014 dollars) [31]. While the 1971 NCP RFC was the first of several RFCs [73], it established the NIDR's research priorities for years [29].

The research priorities in the 1971 NCP RFC largely reflected the research priorities identified at the October 1969 NIDR Caries Task Force Steering Committee meeting (compare columns C and G in Table 3). Despite being published nearly a year after the NIDR Caries Task Force Role of Human Foodstuffs in Caries Workshop Conference (Table 1), the 1971 NIDR RFC omitted developing a standardized model to identify the cariogenicity of foods as a research priority.

Comparison of the research priorities identified by ISRF and submitted to the NIDR in 1969 (Table 3, column E) with those published by the NIDR in its 1971 NCP RFC (column G) shows that ISRF and the NIDR research priorities were largely aligned. Indeed, a side-by-side comparison of overlapping text from the ISRF submission to the NIDR, *Dental Caries Research—1969* [46], and the 1971 NCP RFC, *Opportunities for Participation in the National Caries Program* [30], reveals that 78% of the ISRF submission to the NIDR was directly incorporated into the 1971 NCP RFC. (S1 Table provides the actual text from the ISRF submission and 1971 NCP RFC.) Of the 274 total lines in the 1971 NCP RFC describing research priorities, 110 lines, or 40%, were taken verbatim or closely paraphrased from the ISRF submission. Of these 110 lines, 34% were copied verbatim from the ISRF report, and 66% were paraphrased.

Discussion

This study analyzes a series of papers discussing previously undocumented cane and beet sugar industry activities between 1959 and 1971 regarding strategies to influence the research priorities of the NIDR's 1971 NCP. The documents show that the sugar industry knew that sugar caused dental caries as early as 1950 and did not attempt to deny the causative role of sucrose in tooth decay. Instead, through trade associations, the sugar industry adopted a strategy to deflect attention to public health interventions that would reduce the harm of sugar consumption, rather than restricting intake.

After the NIDR announced it was considering a research program to eradicate dental caries in 1966, the sugar industry used tactics designed to protect sucrose sales. In collaboration with the chocolate and confectionary industries, SRF funded research that supported the idea that enzymes and a tooth decay vaccine could be developed that could eradicate dental decay without requiring sugar restrictions. ISRF conducted reviews of the dental caries literature to identify potential interventions that might reduce the health harms of sugar consumption other than by restricting sugar intake. ISRF cultivated relationships with the NIDR leadership through meetings with the Caries Task Force chairman and through a consultation with members of the NCP steering committee charged with selecting research priorities. A sugar industry report

submitted to the NIDR became the basis for the research priorities published in the first NCP RFC.

While not officially recognized as participating in the NIDR Caries Task Force, the sugar industry effectively contributed to the research priorities developed for the launch of the NCP. Research priorities identified in the first NIDR NCP RFC focused on sugar harm reduction strategies, as opposed to sugar restriction, and were strongly aligned with sugar industry research priorities. The NIDR, like ISRF, took the position that sugar restriction was impractical.

The first policies related to the declaration of conflicts of interest for federal advisory committees were implemented in the early 1960s [74]. Prior to that, concern that industry interests were a threat to scientific integrity was not a majority view [75]. Significant consumer concern about corporate influence on expert committees would not surface until the 1970s, after the launch of the NCP. By contrast, in 2015, the NIH had an entire program dedicated to ethical contact within its institutes [76] because of the greater awareness of industry conflicts of interest and how they can adversely impact the scientific enterprise.

The 1970s Missed Opportunity

The majority of the research priorities promoted by the sugar industry and those selected for the 1971 NCP RFC failed to lead to widespread application [31]. By 1976, clinical studies of dextranase mouth rinses in humans had failed to duplicate the success of using dextranases to inhibit new dental caries in experimental animals [31]. The NIDR found that the pharmaceutical industry had limited interest in research, development, and distribution of antimicrobial agents, because of the high cost of regulatory approval by the Food and Drug Administration (FDA) and doubts about identifying an agent that would be successful on a large scale [31]. By 1977, NCP researchers had found that their plan to substitute sucrose with a mixture of glucose and fructose "would effect little reduction in food cariogenicity" [29]. In addition, by 1978, the NIDR had terminated clinical trials on phosphates added to foods because they were ineffective [31].

The most successful interventions selected for funding following the 1971 NCP RFP were topical fluoride and sealants [31]. While a 1980 prevalence survey found that the burden of dental disease in children had decreased by more than 30% since the last survey in 1971–1973, 64% of children still exhibited dental caries, far short of the NCP's founding goal of eradicating the disease [31].

It is not clear why the NIDR adopted the position in 1969 that reducing sugar intake as a public health measure was impractical. Proposals centered on ways to limit sucrose consumption were just around the corner. In its multi-year review of foods generally recognized as safe initiated in 1969, the FDA deemed sucrose consumption at 1976 levels as unsafe for teeth [77]. In the coming years, the FDA would consider food labels "to warn against the hazards to the teeth of consuming a particular product" and debate whether warning labels should be placed on foods based on the percentage of sugar content, or on some measure of cariogenic potential [78].

When reflecting on the NCP in 1990, Basil Bibby, a member of the Caries Task Force Steering Committee, noted that the NIDR approved only "one or two small research grants" related to food cariogenicity compared to the "hundreds of generous awards [that] were made for investigations with so-called high scientific content" [79]. He also noted that since the NIDR was the major funding source for dental research in the US, "the failure of the National Institute for Dental Research to support research on foods meant that there was no group of investigators in the United States who had enough financial support to undertake significant research on food cariogenicity" [79].

In 1977, the NIDR finally moved to develop a standardized animal model to identify the tooth-decay-causing potential of foods "with the objective of its being widely accepted in industry, and in regulatory agencies and in academic research, as a basis for distinguishing cariogenic from non-cariogenic snacks" [29]. While research on an animal model was initiated at the NIDR [29], the bulk of the research was conducted outside the NIDR, largely funded by the American Dental Association Health Foundation [80]. Based on the promise of the development of a standardized model to identify harmful foods, in 1978 the US Federal Trade Commission proposed restrictions on advertising cariogenic products to children [81]. The first US Department of Health and Human Services Healthy People objectives, issued in 1980, proposed banning cariogenic products from schools as a means to control dental caries [82]. While lobbying efforts of the food, advertising, and broadcasting industries were a major reason for the failure of the FDA, Federal Trade Commission, and Healthy People proposals, another common factor cited for these policy failures is the lack of a standardized model to identify foods harmful to teeth [78,81,83].

With industry input, consensus was finally achieved on a standard method to screen foods for cariogenicity at a conference sponsored by the Foods, Nutrition and Dental Health Program of the American Dental Association in 1985, but only to support claims that food products were safe for teeth [84]. In 1996, the FDA began allowing health claims (i.e., "does not promote tooth decay") on food products containing sugar substitutes based on a standard screening method for cariogenicity [85]. The FDA did not, however, require disclosure or labeling of harmful foods. In 1999, a group of clinicians and dental scientists updated the methodology agreed upon in 1985 with the aim of identifying which methods were "suitable as research tools but also for regulatory assessments" [86]. However, the use of these methods to identify foods harmful to teeth remained controversial [87].

With the implementation of the nutrition facts panel on packaged food products in 1993, the FDA required the declaration of total sugars [88], a requirement that remained unchanged as of January 2015. As of January 2015, the FDA was considering a proposed rule to require disclosure of added sugars on the nutrition facts panel [88], and SA was opposing it, citing "the lack of science to justify 'added sugars' labeling" [89].

Comparison to the Tobacco Industry

The sugar industry formed SRF in 1943 to fund research that supported the industry position [34], 11 years before the creation of the Tobacco Industry Research Committee (TIRC) in 1954 to play a similar role for the tobacco industry [90]. In 1954, the TIRC hired SRF's first scientific director, Robert Hockett, to serve as the TIRC's associate scientific director [91], where he was positioned to help the tobacco industry learn key science manipulation tactics from the sugar industry.

At the same time that the NIDR was planning the NCP, the National Cancer Institute (NCI) was pursuing its Smoking and Health Program [92–94]. Like NCP, which focused on sugar harm reduction strategies, the Smoking and Health Program focused on harm reduction strategies with the primary goal of developing a safe cigarette [93]. The NCI invited tobacco industry representatives to join the NCI's Tobacco Working Group (TWG), the planning committee for the effort to develop a less hazardous cigarette [93]. The NCI did so on the assumption that tobacco manufacturers were interested in promoting new, safer cigarettes and had product expertise the NCI lacked [94]. The NCI also believed industry participation was advantageous because implementation would fall to tobacco companies and, if approached in a positive way, the companies would agree to collaborate [94]. The willingness of the NIDR leaders to interact with the sugar industry during planning for the NCP may have reflected similar

thinking, particularly because responsibility for manufacturing and incorporating additives to reduce the risk of dental caries would fall to food and pharmaceutical industries.

The tobacco industry used its involvement in the TWG to oppose funding of projects, such as smoking cessation programs, that were seen as a threat to industry interests [94]. The tobacco industry also withheld knowledge about the biological effects of cigarette smoke and human smoking behavior, which negatively impacted the NCI's efforts [94]. Indeed, industry use of the TWG to block effective tobacco control strategies was cited by federal Judge Gladys Kessler in her 2006 ruling that the major cigarette companies and their research and lobbying organizations had formed an illegal enterprise to defraud the public in violation of the Racketeer Influenced and Corrupt Organizations Act [95].

Litigation against tobacco companies has been a major factor in achieving meaningful policy change. Successful litigation could not have been achieved without industry documents research illuminating the strategies and tactics of tobacco companies. This analysis demonstrates that sugar industry documents research has the potential to define industry strategies and tactics, which may potentially prove useful in future litigation.

Limitations

While we were fortunate to discover the Roger Adams papers, we recognize that it provides a narrow window into the activities of just one sugar industry trade association, particularly because other industries had an interest in the outcome of the NCP, including the chocolate and confectionary industries, the pharmaceutical industry, and food companies interested in developing food additives and sugar substitutes. To help compensate for limited access to industry documents, we used other historical materials to cross-validate findings as they emerged throughout the analysis. Another limitation was that we could not interview key actors.

Conclusion

This historical example illustrates how industry protects itself from potentially damaging research, which can inform policy makers today. While it may be valuable in theory for the industry to contribute data about their products to the research community, industry should not have the opportunity to influence public health research priorities [94]. Regulatory science to support sensible and defensible policies to limit added sugar consumption was not pursued in the 1970s because of the alignment of the NIDR's research priorities with those of the sugar industry. Actions taken by the sugar industry to impact the NIDR's NCP research priorities, which echo those of the tobacco industry, should be a warning to the public health community. The sugar industry's current position—that public health recommendations to reduce dental caries risk should focus on sugar harm reduction as opposed to sugar restrictions—is grounded in more than 60 years of protecting industry interests. Industry opposition to current policy proposals—including a WHO guideline on sugars proposed in 2014 and changes to the nutrition facts panel proposed in 2014 by the FDA—should be carefully scrutinized to ensure that industry interests do not supersede public health goals.

Supporting Information

S1 Table. Comparison of ISRF's submission to the NIDR Caries Task Force, *Dental Caries Research—1969*, to NIDR's 1971 National Caries Program request for contracts, *Opportunities for Participation in the National Caries Program*.
(PDF)

Acknowledgments

We thank Ernest Newbrun, Aubrey Sheiham, Ben Chaffee, Lauren Lempert, Rachel Barry, Lauren Dutra, Margaret Kulik, Randy Uang, and Clayton Velicer for helpful comments on the manuscript. We thank Linda Stahnke, Cara Bertram, and Willam Maher at the University of Illinois Archives for their assistance with the Roger Adams papers. We thank George Coy for his assistance locating documents related to the NCP at NIDCR.

Author Contributions

Conceived and designed the experiments: CEK SAG LAS. Performed the experiments: CEK. Analyzed the data: CEK SAG LAS. Wrote the first draft of the manuscript: CEK. Contributed to the writing of the manuscript: CEK SAG LAS. Agree with manuscript results and conclusions: CEK SAG LAS. All authors have read, and confirm that they meet, ICMJE criteria for authorship.

References

1. Sheiham A (2001) Dietary effects on dental diseases. Public Health Nutrition 4: 569–591. PMID: 11683551
2. Scientific Advisory Committee on Nutrition (2014) Draft carbohydrates and health report—scientific consultation: 26 June to 1 September 2014. http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/339771/Draft_SACN_Carbohydrates_and_Health_report_consultation.pdf. Accessed 30 June 2014.
3. (2003) Joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases. WHO Technical Report Series No. 916. http://whqlibdoc.who.int/trs/who_trs_916.pdf. Accessed 20 October 2014.
4. World Health Organization Nutrition Guideline Advisory Group (2014) Guideline: sugars intake for adults and children—draft guidelines on free sugars released for public consultation, 5 March 2014. Geneva: World Health Organization.
5. Food and Agriculture Organization of the United Nations (2014) Food-based dietary guidelines. http://www.fao.org/ag/humannutrition/nutritioneducation/fbdg/en/. Accessed 20 October 2014.
6. World Sugar Research Organisation (2012) About WSRO. http://www.wsro.org/AboutWSRO.aspx. Accessed 7 March 2014.
7. Norum KR (2005) World Health Organization's global strategy on diet, physical activity and health: the process behind the scenes. Food Nutr Res 49: 83–88.
8. World Health Organization (2004) Global strategy on diet, physical activity and health. http://www.who.int/dietphysicalactivity/strategy/eb11344/strategy_english_web.pdf. Accessed 19 December 2014.
9. World Sugar Research Organisation (2014) Comments from World Sugar Research Organisation on WHO draft "Guideline: Sugars Intake for Adults and Children.". http://www.wsro.org/Portals/12/Docs/public/documents/News/FINAL%20WSRO%20Comments%20on%20Draft%20WHO%20Guideline%20on%20sugars.pdf. Accessed 30 January 2015.
10. The Sugar Association (2014) Draft guidelines on free sugars released for public consultation, 5 March 2014: "Guideline: Sugars Intake for Adults and Children." http://www.sugar.org/wp-content/uploads/2014/03/Sugar-Association-Comments-Sugars-Intake-Draft-Guidelines.pdf. Accessed 22 August 2014.
11. The Sugar Association (2014) The Sugar Association voices concern regarding the World Health Organization (WHO) draft guideline development process and lack of transparency. http://www.sugar.org/sugar-association-voices-concern-regarding-world-health-organization-draft-guideline-development-process-lack-transparency/. Accessed 12 October 2014.
12. Briscoe AC, Gaine PC (2014 Aug 28) [Letter to Margaret Chan, Director General, World Health Organization.] Washington (District of Columbia): The Sugar Association. http://www.sugar.org/wp-content/uploads/2014/09/WHO-Letter-Signed-8-28-14.pdf. Accessed 10 October 2014.
13. Cottrell RC (2014) Letter to the Editor, "Effect on caries of restricting sugars intake: systematic review to inform WHO guidelines." J Dent Res 93: 530. doi: 10.1177/0022034514526408 PMID: 24595636
14. Lesser LI, Ebbeling CB, Goozner M, Wypij D, Ludwig DS (2007) Relationship between funding source and conclusion among nutrition-related scientific articles. PLoS Med 4: e5. PMID: 17214504

15. Brownell KD, Warner KE (2009) The perils of ignoring history: big tobacco played dirty and millions died. How similar is big food? Milbank Q 87: 259–294. doi: 10.1111/j.1468-0009.2009.00555.x PMID: 19298423

16. Taubes G, Couzens CK (2012) Big sugar's sweet little lies: how the industry kept scientists from asking, does sugar kill? Mother Jones. http://www.motherjones.com/environment/2012/10/sugar-industry-lies-campaign. Accessed 17 October 2014.

17. Moodie R, Stuckler D, Monteiro C, Sheron N, Neal B, et al. (2013) Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. Lancet 381: 670–679. doi: 10.1016/S0140-6736(12)62089-3 PMID: 23410611

18. Bes-Rastrollo M, Schulze MB, Ruiz-Canela M, Martinez-Gonzalez MA (2013) Financial conflicts of interest and reporting bias regarding the association between sugar-sweetened beverages and weight gain: a systematic review of systematic reviews. PLoS Med 10: e1001578. doi: 10.1371/journal.pmed.1001578 PMID: 24391479

19. Nestle M (2013) Food politics: how the food industry influences nutrition and health. Berkeley (California): University of California Press.

20. Brownell KD, Horgen KB (2004) Food fight: the inside story of the food industry, America's obesity crisis, and what we can do about it. Chicago: Contemporary Books.

21. Freudenberg N (2014) Lethal but legal: corporations, consumption, and protecting public health. Oxford: Oxford University Press.

22. The PLOS Medicine Editors (2012) PLOS Medicine series on big food: the food industry is ripe for scrutiny. PLoS Med 9: e1001246. doi: 10.1371/journal.pmed.1001246 PMID: 22723749

23. Todd JS, Rennie D, McAfee RE, Bristow LR, Painter JT, et al. (1995) The Brown and Williamson documents: where do we go from here? JAMA 274: 256–258. PMID: 7609236

24. Eubanks SY, Glantz SA (2013) Bad acts: the racketeering case against the tobacco industry. Washington (District of Columbia): American Public Health Association.

25. World Health Organization (2003) WHO framework convention on tobacco control. http://whqlibdoc.who.int/publications/2003/9241591013.pdf?ua=1. Accessed 20 October 2014.

26. Bero LA (2003) Implications of the tobacco industry documents for public health and policy. Annu Rev Public Health 24: 267–288. PMID: 12415145

27. California Department of Health Services Tobacco Control Section (1998) Model for change: the California experience in tobacco control. Sacramento: California Department of Health Services. http://www.cdph.ca.gov/programs/tobacco/Documents/CTCPmodelforchange1998.pdf. Accessed 2 October 2014.

28. Couzens CK (2012) How a former dentist drilled the sugar industry. Mother Jones. http://www.motherjones.com/environment/2012/10/former-dentist-sugar-industry-lies. Accessed 22 August 2014.

29. Rogers WE (1983) The National Caries Program: the first ten years, a brief history of the National Caries Program at the National Institute of Dental Research. Washington (District of Columbia): US Government Printing Office.

30. National Institute of Dental Research (1971) Opportunities for participation in the National Caries Program. http://catalog.hathitrust.org/Record/003436264. Accessed 16 May 2014.

31. Harris RR (1992) Dental science in a new age: a history of the National Institute of Dental Research. Ames (Iowa): Iowa State University Press.

32. Centers for Disease Control and Prevention Division of Oral Health (2013) Preventing dental caries with community programs. http://www.cdc.gov/oralhealth/publications/factsheets/dental_caries.htm. Accessed 23 October 2014.

33. (1889–1971) Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives. http://archives.library.illinois.edu/ead/ua/1505023/1505023f.html. Accessed 10 October 2010.

34. Sugar Research Foundation (1945) Some facts about the Sugar Research Foundation, Inc. and its prize award program. New York: Sugar Research Foundation.

35. The Sugar Association (1976) The Sugar Association, Inc. Board of Directors Meeting October 14, 1976 Scottsdale, Arizona. Records of the Great Western Sugar Company. Fort Collins (Colorado); Agricultural and Natural Resources Archive, Colorado State University.

36. The Sugar Association (1978) The Sugar Association, Inc. Annual Meeting of Members May 11, 1978, Washington, D.C. Records of the Great Western Sugar Company. Fort Collins (Colorado): Agricultural and Natural Resources Archive, Colorado State University.

37. Adams R (1959) Letter to Ernest W. Greene, President of The Sugar Association (September 17). In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

38. Ross P (1968) Letter to Roger Adams of Sugar Research Foundation Scientific Advisory Board (October 3) In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

39. Adams R (1971) Letter to John L. Hickson, Vice President of International Sugar Research Foundation (February 26). In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

40. National Institute of Dental Research (1970) Oral disease: target for the 70's: five-year plan of the National Institute of Dental Research for optimum development of the nation's dental research effort. http://catalog.hathitrust.org/Record/003253592. Accessed 13 May 2014.

41. National Institute of Dental Research (1970) A National Caries Program of the National Institute of Dental Research: ten-year program of research and development. Bethesda (Maryland): US Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health.

42. Scherp HW (1970) Introduction: why another conference? J Dent Res 49: 1191. PMID: 5274311

43. Bibby BG (1970) Methods for comparing the cariogenicity of foodstuffs. J Dent Res 49: 1334–1336. PMID: 4991889

44. (1970) Discussion. J Dent Res 49: 1337–1338.

45. National Caries Program Evaluation Project (1980) Evaluation of the National Institute of Dental Research National Caries Program. Bethesda (Maryland): US Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health.

46. International Sugar Research Foundation (1969) Dental caries research—1969. In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

47. International Sugar Research Foundation (1969) The International Sugar Research Foundation quadrennial report of research for the years 1965–1969. In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

48. Johnson V (1968) Letter to Scientific Advisory Board of the Sugar Research Foundation (November 19). In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

49. Ross P (1968) Philip Ross, curriculum vitae. In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

50. International Sugar Research Foundation (1970) International Sugar Research Foundation special report: dental caries. In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

51. International Sugar Research Foundation (1969) International Sugar Research Foundation symposium on the status of research in sucrochemistry, diet and heart disease, obesity, dental caries, and clinical nutrition. In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

52. International Sugar Research Foundation (1969) International Sugar Research Foundation research symposium: seeking new approaches to old problems. In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

53. International Sugar Research Foundation (1969) International Sugar Research Foundation dental caries task force October 20, 1969. In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

54. Miller WD (1890) The micro-organisms of the human mouth: the local and general diseases which are caused by them. Philadelphia: S. S. White Dental Manufacturing Company.

55. Fitzgerald R, Jordan H, Stanley H, Poole W, Bowler A (1960) Experimental caries and gingival pathologic changes in the gnotobiotic rat. J Dent Res 39: 923–935. PMID: 13700062

56. Fitzgerald RJ (1960) Demonstration of the etiologic role of streptococci in experimental caries in the hamster. J Am Dent Assoc 61: 9–13. PMID: 13823312

57. Fitzgerald R, Spinell D, Stoudt T (1968) Enzymatic removal of artificial plaques. Arch Oral Biol 13: 125–129. PMID: 5237550

58. Stephan R (1940) Changes in hydrogen-ion concentration on tooth surfaces and in carious lesions. J Am Dent Assoc 27: 718–723.

59. Stephan RM (1944) Intra-oral hydrogen-ion concentrations associated with dental caries activity. J Dent Res 23: 257–266.

60. Preston AJ, Edgar WM (2005) Developments in dental plaque pH modelling. J Dent 33: 209–222. PMID: 15725521

61. Stephan RM (1966) Effects of different types of human foods on dental health in experimental animals. J Dent Res 45: 1551–1561. PMID: 5225331

62. Newbrun E (1967) Sucrose, the arch criminal of dental caries. Odontol Revy 18: 373. PMID: 5234965

63. Sugar Research Foundation (1950) Progress and prospects, scientific research in physiology, nutrition and special uses of sugar: seventh annual report, 1950. New York: Sugar Research Foundation.

64. Fitzgerald R, Keyes PH, Stoudt TH, Spinell DM (1968) Effects of a dextranase preparation on plaque and caries in hamsters, a preliminary report. J Am Dent Assoc 76: 301.

65. Fitzgerald R, Keyes P (1962) Attempted immunization of albino hamsters against induced dental caries [abstract]. 40th General Meeting of the International Association for Dental Research; March 1962; St. Louis, MO, US.

66. (1968 Nov 16) These monkeys may save your teeth. Montreal Gazette. Montreal: Postmedia Network.

67. Cheek DW (1974) Sugar Research, 1943–1972. Bethesda (Maryland): International Sugar Research Foundation.

68. International Sugar Research Foundation (1968) The International Sugar Research Foundation, Inc. announces its move to new headquarters. In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

69. Ross P (1969) Memorandum to Executive Committee regarding Research Program (August 11). In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

70. Ross P (1969) Letter to Roger Adams, ISRF Scientific Advisory Board Member (November 14). In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

71. International Sugar Research Foundation (1969) Summary of the discussion and recommendations of the International Sugar Research Foundation panel meeting of the Dental Caries Task Force, October 20–21, 1969. In: Roger Adams: an inventory of the papers of Roger Adams at the University of Illinois Archives. Record Series Number 15/5/23. Urbana (Illinois): University of Illinois Archives.

72. (1970) Table of contents. J Dent Res 49: 1190–1191.

73. US Department of Health, Education, and Welfare (1972) National Caries Program: National Institute of Dental Research—status report 1972. Bethesda (Maryland): US Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health.

74. Lo B, Field MJ, Institute of Medicine, Committee on Conflict of Interest in Medical Research, Education, and Practice (2009) Conflict of interest in medical research, education, and practice. Washington (District of Columbia): National Academies Press.

75. Parascandola M (2007) A turning point for conflicts of interest: the controversy over the National Academy of Sciences' first conflicts of interest disclosure policy. J Clin Oncol 25: 3774–3779. PMID: 17704427

76. National Institutes of Health (2014) NIH ethics program overview. https://ethics.od.nih.gov/overview.htm. Accessed 9 February 2015.

77. US Department of Health and Human Services (2013) Food and Drug Administration Select Committee on GRAS Substances (SCOGS) opinion: sucrose. http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/SCOGS/ucm260083.htm. Accessed 24 March 2014.

78. Miller SA (1981) Sugar, oral health and regulation: a strategy for prevention of oral disease. In: Hefferen JJ, Koehler MS, editors. Foods, nutrition and dental health. Park Forest South (Illinois): Pathotox Publishers. pp. 385–394.

79. Bibby BG (1990) Food and the teeth. New York: Vantage.

80. Hefferen JJ, Koehler MS, editors (1981) Foods, nutrition and dental health. Park Forest South (Illinois): Pathotox Publishers. 417 p.

81. Westen T (2006) Government regulation of food marketing to children: the Federal Trade Commission and the kid-vid controversy. Loyola Los Angel Law Rev 39: 79.

82. US Department of Health and Human Services (1980) Promoting health/preventing disease: objectives for the nation. Washington (District of Columbia): Department of Health and Human Services, Public Health Service.

83. United States Office of Disease Prevention and Health Promotion (1986) The 1990 health objectives for the nation: a midcourse review. Washington (District of Columbia): US Department of Health and Human Services, Public Health Service.

84. Hefferren J, editor (1986) Scientific consensus conference on methods for assessment of the cariogenic potential of foods: November 17–21, 1985, San Antonio, Texas: proceedings. J Dent Res 65S. 72 p.

85. US Food and Drug Administration (2014) Code of Federal Regulations Title 21, Volume 2. Part 101—food labeling. Subpart E—specific requirements for health claims. Sec. 101.80. Health claims: dietary noncariogenic carbohydrate sweeteners and dental caries. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=101.80. Accessed 20 October 2014.

86. Curzon ME, Hefferren JJ (2001) Modern methods for assessing the cariogenic and erosive potential of foods. Br Dent J 191: 41–46. PMID: 11491478

87. Zero D (2004) Sugars: the arch criminal? Caries Res 38: 277–285. PMID: 15153701

88. US Food and Drug Administration (2014) Proposed changes to the nutrition facts label. http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm385663.htm. Accessed 18 December 2014.

89. The Sugar Association (2014) The Sugar Association calls for withdrawal of 'added sugars' labeling proposal in comments filed to FDA. http://www.sugar.org/sugar-association-calls-withdrawal-added-sugars-labeling-proposal-comments-filed-fda/. Accessed 18 December 2014.

90. Glantz SA, Slade J, Bero LA, Hanauer P, Barnes DE (1996) The cigarette papers. Berkeley: University of California Press.

91. Tobacco Industry Research Committee (1954 Dec 6) Scientific associate named by tobacco research group. http://legacy.library.ucsf.edu/tid/noe6aa00. Accessed 19 December 2014.

92. Gori GB (2000) Virtually safe cigarettes: reviving an opportunity once tragically rejected. Amsterdam: IOS Press.

93. Parascandola M (2005) Science, industry, and tobacco harm reduction: a case study of tobacco industry scientists' involvement in the National Cancer Institute's Smoking and Health Program, 1964–1980. Public Health Rep 120: 338–349. PMID: 16134578

94. Parascandola M (2005) Lessons from the history of tobacco harm reduction: the National Cancer Institute's Smoking and Health Program and the "less hazardous cigarette". Nicotine Tob Res 7: 779–789. PMID: 16191749

95. US Court of Appeals for the District of Columbia Circuit (2009) United States v. Philip Morris USA Inc., 449 F. Supp. 2d 1, 157 (D.D.C. 2006), aff'd in part & vacated in part, 566 F.3d 1095 (D.C. Cir. 2009) (per curiam), cert. denied, 561 US ___, 130 S. Ct. 3501 (2010).

PLOS | MEDICINE

Editors' Summary

Background.

Tooth decay (dental caries) is the leading chronic disease of children and adolescents. Although largely preventable, 42% of children in the US have some decay in their baby (primary) teeth, and 59% of adolescents have cavities in their permanent teeth. Tooth decay occurs when the hard enamel covering the tooth surface is damaged by acid, which is produced by bacteria in the mouth. Plaque, a sticky substance of bacteria, food particles, and saliva, constantly forms on teeth. When you eat food—particularly sugary foods and drinks—the bacteria in plaque produce acids that attack the tooth enamel. The stickiness of the plaque keeps the acids in contact with the teeth. Plaque buildup can be prevented by regular brushing and flossing. Dentists can detect tooth decay before it causes toothache through visual examination or by taking dental X-rays, and can treat the condition by removing the decay and plugging the hole with a "dental filling." However, if the decay has damaged the nerve in the center of the tooth, root canal treatment or removal of the tooth may be necessary.

Why Was This Study Done?

Experts generally agree that sugars play a causal role in tooth decay. Consequently, in 2014, the World Health Organization (WHO) issued a draft guideline that recommended a daily limit on the consumption of "free" sugars (sugars added to food by manufacturers, cooks, or consumers). Also in 2014, the US Food and Drug Administration (FDA) proposed that the nutrition facts panels on US packaged food products should list added sugars. As with similar proposals made in the past, the World Sugar Research Organisation, a trade organization that represents companies with economic interests in sugar production, is challenging these proposals, arguing that, rather than trying to limit sugar intake, public health interventions to prevent tooth decay should focus on reducing the harms of sugar consumption. Here, the researchers explore how the sugar industry has historically sought to undermine or subvert policies to restrict sugar consumption, by examining internal industry documents related to the launch of a targeted research program to identify interventions to eradicate tooth decay—the National Caries Program (NCP)—by the US National Institute of Dental Research (NIDR) in 1971.

What Did the Researchers Do and Find?

The researchers analyzed an archive of 319 internal sugar industry documents from 1959 to 1971 (the "Roger Adams papers") and NIDR documents to explore how the sugar industry sought to influence the setting of research priorities for the NCP. Their analysis indicates that, as early as 1950, sugar industry trade organizations had accepted that sugar damaged teeth and had recognized that the dental community favored restricting sugar intake as a key way to control caries. The sugar industry therefore adopted a strategy to deflect attention towards public health interventions that would reduce the harms of sugar consumption. This strategy included tactics such as funding research into enzymes that break up dental plaque and into a vaccine against tooth decay, and cultivating relationships with the NIDR leadership. Notably, 78% of a report submitted to the NIDR by the sugar industry was directly incorporated into the NIDR's first request for research proposals for the NCP, and research that could have been harmful to sugar industry interests

(specifically, research into methods to measure the propensity of specific foods to cause caries) was omitted from the research priorities identified at the launch of the NCP.

What Do These Findings Mean?

These findings, although limited by the researchers' reliance on a single source of industry documents and by the absence of interviews with key actors in the launch of the NCP, reveal an alignment of research agendas between the NIDR and the sugar industry in the early 1970s. The findings also suggest that the NCP was a missed opportunity to develop a scientific understanding of how to restrict sugar consumption to prevent tooth decay. Indeed, although tooth decay declined by 20% between 1971/1973 and 1980, 64% of children still developed caries a decade after the NCP was launched. Most importantly, these findings illustrate how the sugar industry has protected itself from potentially damaging research in the past; a similar approach has also been taken by the tobacco industry. These findings highlight the need to carefully scrutinize industry opposition to the proposed WHO and FDA guidelines on sugar intake and labeling, respectively, to ensure that industry interests do not interfere with current efforts to improve dental public health.

Additional Information.

Please access these websites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1001798.

- The US National Institute of Dental and Craniofacial Research (the successor to the NIDR) provides detailed information on tooth decay (in English and Spanish)
- The US Centers for Disease Control and Prevention also provides information on dental caries
- The UK National Health Service Choices website provides detailed information about all aspects of tooth decay; it also provides an analysis of a recent news report concerning research supporting the proposed WHO guideline for limiting sugar intake
- MedlinePlus provides links to additional information about tooth decay (in English and Spanish)
- Information about the 2014 WHO draft guideline on sugar intake and about the changes proposed to the nutrition facts label by the FDA are available (in English and Spanish)

11.2 Lessons Learned from the Gene Therapy Trial for Ornithine Transcarbamylase Deficiency

James M. Wilson

Wilson, J. Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency. *Molecular Genetics and Metabolism* 96, 151–157 (2009).

Molecular Genetics and Metabolism 96 (2009) 151–157

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Commentary

Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency

James M. Wilson *

Department of Pathology and Laboratory Medicine, University of Pennsylvania, Suite 2000 TRL, 125 S. 31st Street, Philadelphia, PA 19104-3403, USA

ARTICLE INFO

Article history:
Received 10 October 2008
Received in revised form 23 December 2008
Accepted 24 December 2008
Available online 10 February 2009

Keywords:
Gene therapy
Ornithine transcarbamylase deficiency
Clinical trial

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

* Fax: +1 215 898 6588.
E-mail address: wilsonjm@mail.med.upenn.edu

1096-7192/
doi:10.1016/j.ymgme.2008.12.016

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.

References

[1] J.E. Wraith, Ornithine carbamoyltransferase deficiency, Arch. Dis. Child. 84 (2001) 84–88.
[2] A.A. Busuttil, J.A. Goss, P. Seu, T.S. Dulkanchainun, G.S. Yanni, S.V. McDiarmid, R.W. Busuttil, The role of orthotopic liver transplantation in the treatment of ornithine transcarbamylase deficiency, Liver Transpl. Surg. 4 (1998) 350–354.
[3] S. Brusilow, J. Tinker, M.L. Batshaw, Amino acid acylation: a mechanism of nitrogen excretion in inborn errors of urea synthesis, Science 207 (1980) 659–661.
[4] X. Ye, M.B. Robinson, M.L. Batshaw, E.E. Furth, I. Smith, J.M. Wilson, Prolonged metabolic correction in adult ornithine transcarbamylase-deficient mice with adenoviral vectors, J. Biol. Chem. 271 (1996) 3639–3646.
[5] X. Ye, M.B. Robinson, C. Pabin, T. Quinn, A. Jawad, J.M. Wilson, M.L. Batshaw, Adenovirus-mediated in vivo gene transfer rapidly protects ornithine transcarbamylase-deficient mice from an ammonium challenge, Pediatr. Res. 41 (1997) 527–534.
[6] F.A. Nunes, E.E. Furth, J.M. Wilson, S.E. Raper, Gene transfer into the liver of nonhuman primates with E1-deleted recombinant adenoviral vectors: safety of readministration, Hum. Gene Ther. 10 (1999) 2515–2526.
[7] Y. Yang, H.C. Ertl, J.M. Wilson, MHC class I-restricted cytotoxic T lymphocytes to viral antigens destroy hepatocytes in mice infected with E1-deleted recombinant adenoviruses, Immunity 1 (1994) 433–442.
[8] G.P. Gao, Y. Yang, J.M. Wilson, Biology of adenovirus vectors with E1 and E4 deletions for liver-directed gene therapy, J. Virol. 70 (1996) 8934–8943.
[9] S.E. Raper, Z.J. Haskal, X. Ye, C. Pugh, E.E. Furth, G.P. Gao, J.M. Wilson, Selective gene transfer into the liver of non-human primates with E1-deleted, E2A-defective, or E1–E4 deleted recombinant adenoviruses, Hum. Gene Ther. 9 (1998) 671–679.
[10] S.E. Raper, M. Yudkoff, N. Chirmule, G.P. Gao, F. Nunes, Z.J. Haskal, E.E. Furth, K.J. Propert, M.B. Robinson, S. Magosin, H. Simoes, L. Speicher, J. Hughes, J. Tazelaar, N.A. Wivel, J.M. Wilson, M.L. Batshaw, A pilot study of in vivo liver-directed gene transfer with an adenoviral vector in partial ornithine transcarbamylase deficiency, Hum. Gene Ther. 13 (2002) 163–175.
[11] N.M. King, O. Cohen-Haguenauer, En route to ethical recommendations for gene transfer clinical trials, Mol. Ther. 16 (2008) 432–438.
[12] S.E. Raper, N. Chirmule, F.S. Lee, N.A. Wivel, A. Bagg, G.P. Gao, J.M. Wilson, M.L. Batshaw, Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer, Mol. Genet. Metab. 80 (2003) 148–158.
[13] M.A. Schnell, Y. Zhang, J. Tazelaar, G.P. Gao, Q.C. Yu, R. Qian, S.J. Chen, A.N. Varnavski, C. LeClair, S.E. Raper, J.M. Wilson, Activation of innate immunity in nonhuman primates following intraportal administration of adenoviral vectors, Mol. Ther. 3 (2001) 708–722.
[14] Y. Zhang, N. Chirmule, G.P. Gao, R. Qian, M. Croyle, B. Joshi, J. Tazelaar, J.M. Wilson, Acute cytokine response to systemic adenoviral vectors in mice is mediated by dendritic cells and macrophages, Mol. Ther. 3 (2001) 697–707.
[15] A.N. Varnavski, R. Calcedo, M. Bove, G. Gao, J.M. Wilson, Evaluation of toxicity from high-dose systemic administration of recombinant adenovirus vector in vector-naive and pre-immunized mice, Gene Ther. 12 (2005) 427–436.
[16] A.N. Varnavski, Y. Zhang, M. Schnell, J. Tazelaar, J.P. Louboutin, Q.C. Yu, A. Bagg, G.P. Gao, J.M. Wilson, Preexisting immunity to adenovirus in rhesus monkeys fails to prevent vector-induced toxicity, J. Virol. 76 (2002) 5711–5719.
[17] D. Shalala, Protecting research subjects–what must be done, N. Engl. J. Med. 343 (2000) 808–810.
[18] D.M. Cain, A.S. Detsky, Everyone's a little bit biased (even physicians), JAMA 299 (2008) 2893–2895.
[19] M.K. Paasche-Orlow, H.A. Taylor, F.L. Brancati, Readability standards for informed-consent forms as compared with actual readability, N. Engl. J. Med. 348 (2003) 721–726.
[20] E.H. Morreim, End-stage heart disease, high-risk research, and competence to consent: the case of the AbioCor artificial heart, Perspect. Biol. Med. 49 (2006) 19–34.

11.3 Patient Perspectives on Physician Conflict of Interest in Industry-Sponsored Clinical Trials for Multiple Sclerosis Therapeutics

Andrew J. Solomon

Solomon, AJ, et al. Patient perspectives on physician conflict of interest in industry-sponsored clinical trials for multiple sclerosis therapeutics. *Multiple Sclerosis Journal* 21(12), 1593–1599 (2015).

MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Patient perspectives on physician conflict of interest in industry-sponsored clinical trials for multiple sclerosis therapeutics

Multiple Sclerosis Journal
2015, Vol. 21(12) 1593–1599
DOI: 10.1177/1352458515569101

Andrew J Solomon, Eran P Klein, John R Corboy and James L Bernat

Abstract

Background: Pharmaceutical industry financial support of physicians, physician practices, and academic departments involved in multicenter industry-sponsored clinical trials of novel therapeutic agents is a relatively new and infrequently acknowledged source of potential physician conflict of interest. Detailed disclosure of these relationships to study participants is not uniformly a part of informed consent and documentation practices.

Objective: To understand attitudes of patients with multiple sclerosis concerning disclosure of potential physician–industry conflicts of interest created by clinical trials and how such disclosures may influence study participation

Methods: An anonymous online instrument was developed.

Results: 597 people with multiple sclerosis participated in the study. The study found that detailed disclosure of conflicts of interest is important to potential participants in industry-sponsored clinical trials for multiple sclerosis therapies and that the presence of these conflicts of interest may influence patients' decisions to participate in these studies.

Conclusions: Findings from this study support a call for uniform guidelines regarding disclosure of physician–industry relationships to prospective research participants for industry-sponsored clinical trials.

Keywords: Multiple sclerosis, clinical trials, conflict of interest, professional conduct and ethics, industry-sponsored clinical trials

Date received: 28 November 2014; accepted: 2 January 2015

Introduction

Disclosure of physician–industry financial relationships – such as physician stock ownership or compensation for consultative activities – has become a standard tool for addressing potential physician conflict of interest (COI).[1–4] Direct industry financial support of physicians, physician practices, and academic departments involved in multicenter industry-sponsored clinical trials (ISCT) of novel therapeutic agents is a relatively new and infrequently acknowledged source of potential physician COI. Detailed disclosure of these relationships to potential study participants is not uniformly included as part of informed consent and documentation practices in ISCT. We conducted a survey of multiple sclerosis (MS) patients to understand patient perspectives on the disclosure of physician compensation for participation in ISCT. MS is a particularly fertile field for the investigation of patient attitudes toward ISCT COI management and disclosure given the rapid development and FDA approval of new therapeutics[5] and a global market value for these therapies estimated at up to US$16bn by 2016.[6]

Methods

An anonymous survey instrument of patient attitudes toward physician–industry relationships created by ISCT for MS was developed by the contributing authors and distributed through SurveyMonkey.com to people self-identifying as having MS. The survey directed respondents to questions based on specific responses, and captured an IP address to prevent multiple submissions by a single individual. The survey instrument was not previously validated. The instrument was reviewed by the University of Vermont

Correspondence to:
Andrew J Solomon
University of Vermont College of Medicine, 1 South Prospect St., Arnold 2, Burlington Vermont, 05401, USA.
andrew.solomon@uvm.edu

Andrew J Solomon
University of Vermont College of Medicine, USA

Eran P Klein
Oregon Health and Sciences University and Portland VA Medical Center, USA; Department of Philosophy, University of Washington, USA

John R Corboy
University of Colorado School of Medicine, USA; Denver Veterans Affairs Medical Center, USA

James L Bernat
Neurology Department, Dartmouth-Hitchcock Medical Center, USA

Table 1. Demographic Data For Survey Participants.

Gender	Female 82% (453) Male 18% (100)
Age	49.7 +/- 11.9
Home State	Oregon 41% (240) Non-Oregon 52% (308)
Years since MS diagnosis	12.8 +/- 9.8
Had participated in ISCT	Yes 13% (76) No 76% (454) Unsure 11%(65)
MS phenotype	RRMS 75% (397) SPMS 15% (85) PPMS 5% (29) PRMS 3% (15) Unknown 5% (26)

MS: multiple sclerosis, ISCT: industry sponsored clinical trial, RRMS: relapsing remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis, PPMS: primary progressive multiple sclerosis, PRMS: progressive relapsing multiple sclerosis.

Institutional Review Board prior to use and determined to be exempt from further formal committee review and approval. Recruitment was conducted through posting of an internet link to the survey in the research section of the National Multiple Sclerosis Society (NMSS) website, and regional NMSS chapters publicized the study on their own local websites, through paper or email newsletters, social media, or individual emails to members. Information about the study was also given to patients during routine clinical visits with one of the authors (AJS) at the University of Vermont Medical Center. Study information was given to patients at the Rocky Mountain Multiple Sclerosis Center at Anschutz Medical Campus in Aurora, Colorado, during routine clinical visits and was also described in a newsletter. The survey was available for completion online exclusively for three months from February 2014 through May 2014. The survey instrument is available as a supplemental file and, because the survey was navigated on the internet and subjects were automatically routed to certain questions, this pdf version of the instrument necessarily contains notation demonstrating the questions displayed to each subject based on their responses.

Results

Demographic data

Table 1 contains demographic data of survey participants. A total of 597 people with MS participated in the study and 552 completed the entire survey. Responses from partially completed surveys were included in the results, and questions not answered were coded as missing.

The Oregon chapter of the NMSS emailed each member individually about this study while other participating state chapters relied on newsletters and social media. Of the respondents, 41% (240) identified Oregon as their home state, 52% (308) identified one of 36 additional US states as home, and 4 identified regions outside of the US. Given the large number of participants from Oregon, their responses were compared to responses from other states. Statistically significant differences were found in response to demographic questions but in no questions regarding ISCT COI. The mean age for Oregon participants was older (52 vs. 48, $p < 0.0001$) and their reported mean duration of diagnosis of MS was longer (14.4 years vs. 11.5 years, $p = 0.0007$). Fewer Oregon respondents identified as having RRMS compared to all other phenotypes of MS (67% vs. 76%, $p = 0.0170$). Oregon respondents were less likely to have participated in an ISCT (10% vs. 16%, $p = 0.02$).

Responses from subjects who had not *participated in an ISCT in the past*

Of the respondents 76% (454) had not participated in an ISCT for a MS medication in the past and 11% (65) were unsure if they had. For the purpose of analysis, these two groups ("non-ISCT respondents") were combined.

Non-ISCT respondents were given a hypothetical scenario which "offered the opportunity to participate in a pharmaceutical company sponsored research study of a new MS medication at your neurologist's office." Among these respondents, 87% (452) thought "a doctor involved in a research study should disclose that they or their office is paid for your participation in the study." Also, 67% (342) thought "a doctor involved in a research study should disclose how they or their office use money they are paid for your participation in the study." These results are represented in Table 2 and compared to the cohort of respondents who had participated in an ISCT in the past.

When respondents who had not participated in an ISCT in the past were offered participation in a hypothetical ISCT, disclosure of a number of additional COI relationships was also important to their decision whether to participate in the study (Table 3). Of the respondents, 79% (405) thought it was either somewhat important or extremely important "to know if

Table 2. MS patients' opinions regarding disclosure of potential COI for ISCT.

	Had not participated in ISCT	Had participated in ISCT
"A doctor involved in a research study should disclose that they or their office is paid for your participation in the study"	87% (452)	75% (44)
"A doctor involved in a research study should disclose how they or their office use money they are paid for your participation in the study"	67% (342)	66% (39)

MS: multiple sclerosis, COI: conflicts of interest, ISCT: industry sponsored clinical trial.

Table 3. Importance of disclosure of COI relationships to subjects with MS when considering participation in an ISCT.

Potential COI	Disclosure is important
Compensation toward PI salary	79% (405)
Previous payments for speaking engagements	61% (302)
Previous payments for consulting	69% (345)
Current payments for speaking engagements	70% (346)
Current payments for consulting	76% (375)

COI: conflicts of interest, MS: multiple sclerosis, ISCT: industry sponsored clinical trial, PI: primary investigator.

the sponsoring pharmaceutical company will because of your participation pay your neurologist money that is used toward their salary" before deciding whether to participate in a study.

Of the non-ISCT respondents, 61% (302) responded that it was either "somewhat important" or "extremely important" to know if a pharmaceutical company "sometime in the past paid your neurologist to give talks about MS to doctors or patients" before deciding whether to participate in a clinical trial. Of the non-ISCT respondents, 69% (345) responded that it was either "somewhat important" or "extremely important" to know if a pharmaceutical company "sometime in the past paid your neurologist to provide advice (consulting) for the drug company." Of the non-ISCT respondents, 70% (346) responded that it was either "somewhat important" or "extremely important" to know if a pharmaceutical company "currently pays your neurologist to give talks about MS to doctors or patients," and 76% (375) responded it was either "somewhat important" or "extremely important" to know if a pharmaceutical company "currently pays your neurologist to provide advice (consulting) for the drug company."

Respondents who had *participated in an ISCT in the past*

Of the survey respondents, 13% (76) had "participated in a pharmaceutical company-sponsored research study of a MS medication" sometime in the past. Of these respondents, 47% (35) participated in the study at a "university," 23% (17) at a "private practice office," 15% (11) at a "private research center," and 16% (12) were "not sure."

Of these respondents who had participated in an ISCT, 75% (44) indicated that "a doctor involved in a research study should disclose that they or their office is paid for your participation in the study" and 66% (39) thought "a doctor involved in a research study should disclose *how* they or their office use the money they are paid for your participation in the study." These results are displayed in Table 2 and compared to respondents who had not participated in a clinical trial in the past.

Respondents who identified their own neurologist as running the study they enrolled in were asked "Did your neurologist ever discuss whether the pharmaceutical company would provide money to run the study or pay researchers?" Of the respondents, 67% (18) responded "No" and 7% (2) "Not sure." Among respondents who were enrolled in a study with a neurologist other than their routine care provider, 50% (24) said "No" and 31% (15) did not recall such a discussion. Of those who recalled such a discussion regarding compensation for the ISCT, 53% (10) affirmed that "having this discussion before I enrolled in the study was: important to me/my decision." Respondents who recalled having a discussion with the primary investigator (PI) about compensation were asked if it was their "understanding that because of your participation

money paid to the neurologist running the study would be used: only for 'overhead' (such as clinic time and space, staff salaries and supplies) associated with your participation." Of the respondents, 53% (8) of subjects who had engaged in this conversation thought that compensation would *only* pay for "overhead."

When asked "Would knowing that the neurologist running the study received money toward their salary from the pharmaceutical company because of your participation have influenced your decision to participate in the study?" 5 (7%) "would probably not have participated" or "would definitely not have participated," and 13 (18%) chose "not sure,". When asked "Would it have changed your decision to participate in the study if the pharmaceutical company also had paid the neurologist running the study to give talks about MS to doctors or patients sometime before the study started," 7 (9%) would "probably not have participated" or "definitely not have participated" and 4 (5%) responded that they "would probably not have participated" or "would definitely not have participated" if the PI was paid to give talks "while you were in the study." When asked "Would it have changed your decision to participate in the study if the pharmaceutical company also had paid the neurologist running the study to provide advice (consulting) sometime before the study started," 9 (12%) responded they either "would probably not have participated" or "would definitely not have participated" and 7 (9%) responded they "would probably not have participated" or "would definitely not have participated" if the PI was paid for such "while you were in the study."

Associations

Respondents who had not participated in an ISCT in the past were more likely to indicate that they thought "a doctor involved in a research study should disclose that they or their office is paid for your participation in the study," 87% (452) vs. 75% (44), $p = 0.0079$. However, respondents who stated they had not participated in an ISCT were just as likely as those who had participated in such a trial to indicate they thought "a doctor involved in a research study should disclose *how* they or their office use the money they are paid for your participation in the study: 66% (39) vs. 67% (342). Responses to duration of MS diagnosis and type of MS were not significantly associated with responses to any questions surrounding disclosure. In the group that had participated in an ISCT in the past, associations between responses were not assessed given the small number in this group.

For respondents who had not participated in an ISCT, women were more likely to respond that it was important "to know if the sponsoring pharmaceutical company will because of your participation pay your neurologist money that is used toward their salary": 81.5% (322) vs. 70.0% (60), $p = 0.0146$. Women were also more likely to say it was either "somewhat important' or "very important" "to know that sometime in the past the pharmaceutical company paid your neurologist to give talks about MS to doctors or patients": 63.3% (250) vs. 47.7% (41), $p = 0.0073$. Women were also more likely to respond that it was either "somewhat important" or "very important" "to know that sometime in the past the pharmaceutical company paid your neurologist to provide advice (consulting) for the drug company" running the study: 71.14% (281) vs. 60.47% (52), $p= 0.0519$, when considering an ISCT. Demographic differences noted above between the group of respondents who lived in Oregon compared to non-Oregon respondents did not have a statistically significant influence on the above associations.

Discussion

ISCT for MS therapeutics involve financial relationships between physicians and industry that lead to improvements in the care of MS patients but that also generate potential COIs. Our study demonstrates the importance of disclosure of information concerning physician COIs in MS ISCT to potential participants, such as who receives compensation, how funds are allocated, and current and prior financial relationships with industry. This perceived importance of COI disclosure is consistent with data from other patient populations.[7–13] Our data suggest that the presence of these COIs may influence participation in MS ISCT. Findings from this study support a call for uniform guidelines regarding disclosure of physician–industry relationships to prospective research participants for ISCT.

A conflict of interest is "a set of conditions in which professional judgment concerning a primary interest (i.e., a patient's welfare, validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)."[4] Contract research organizations are gradually supplanting academia's traditional role in drug development, providing new sources of funding for both academic and non-academic physicians.[14,15] Budgets for ISCTs are negotiated between sponsors and research institutions or sponsors and individual physician researchers, and can be structured to potentially generate financial surpluses on top of compensation for the time and effort of participating physicians, research staff, and payment of "overhead" expenses.[14] In academic centers, such revenue might subsidize various aspects of the research infrastructure,

but some benefits may rebound to individual researchers either directly or indirectly and may support productivity or a base salary of a PI, substitute for revenue-generating clinical care, allow for additional protected academic time for other pursuits, or contribute to salaries of the support staff and research coordinators who contribute clinical and academic efforts beyond a particular ISCT. In non-academic settings, the connection between ISCT payment and physician compensation is perhaps more direct.[16] The extent to which ISCT as a source of revenue, particularly for private practice physicians, leads to the compromising of ethical standards remains a pressing but open question.[16–18]

Data on the disclosure of financial relationships to subjects participating in ISCT is limited. The patient populations studied and the specific types of COIs disclosed vary.[7–13] Respondents in the present survey overwhelmingly favored disclosure of physician financial relationships. This finding adds to emerging data across diverse disease populations indicating that patients considering participation in clinical trials favor disclosure of physician–industry relationships that may represent a COI.[7–13] Potential physician conflicts can be an important piece of information for patients as they weigh the pros and cons of volunteering for a research study and can enhance or preserve trust between a subject and investigator,[9,19] and ensure that patients make well-informed decisions that preserve their autonomy.

Compensation for ISCT for multiple sclerosis in both academic and nonacademic settings may provide incentives to expand recruitment, but this study suggests that the recruitment benefit may come at a cost. Respondents with MS who had never participated in an ISCT indicated that the presence of a potential COI might influence their decision whether to volunteer for an ISCT. Presented with a hypothetical ISCT, a majority felt it important to know about potential COIs, including a PI's salary contribution from study involvement as well as whether a PI had current or prior industry financial relationships. Our findings are in agreement with a large study of 5478 potential research participants where a sizeable minority (up to 20%) of respondents indicated they might not participate in a clinical trial if certain financial COIs, particularly individual investigators' COIs, were present.[13] While some studies have suggested that perceived COIs may not impact willingness to participate in research,[9–11,19–21] these studies also suggest that disease severity and lack of alternative treatment options, particularly in patients with advanced cancer or who were seriously ill, may exert a stronger influence on decisions surrounding clinical trial participation.[10,11,21] The findings of the current study add to the literature indicating that potential physician COIs in ISCTs may not only increase risk for participants and jeopardize scientific integrity,[8,14,19,22] but may also have an adverse effect on recruitment.

Our study has several limitations. Our survey instrument was not validated. The authors designed questions to cover many possible forms of potential COIs that might result from financial relationships created by an ISCT. This inclusive and general language may have precluded a more nuanced understanding of the importance of those types of financial arrangements that result in COIs compared to those that do not. We also acknowledge that certain ISCT relationships can result in a net revenue loss for academic departments or practices. As with all surveys there is potential for selection and recall bias, and studies that present hypothetical decisions for respondents are categorically limited. Although participants heard about the study through their neurologist or the National MS Society web site and were presumably diagnosed accurately, there was also no direct ascertainment of diagnostic validity. Responses may have also been influenced by severity of disability and this was not assessed. We carefully worded survey questions in an attempt to use "neutral" language to eliminate bias. This ideal may not always have been met and alternative phrasing of our questions may have led to different results. Moreover, patients carry biases toward the pharmaceutical industry or physician–pharma relationships that may not have been adequately surveyed. Lastly, the subgroup in our study that had participated in an ISCT in the past and completed the survey was small, and more data are needed from those who are currently participating or have participated in ISCT for MS therapies.

Collaborations between physicians and industry have resulted in the advancement of scientific knowledge and have improved the care of patients with MS. However, changes in how COIs are disclosed and managed in clinical trials for the development of MS therapeutics are needed. Language in typical consent forms such as "the investigator is being paid by the sponsor to conduct the research study" or "the sponsor will pay the clinic or institution where the study is conducted for the costs of running the study" may not be adequate. Lack of detailed COI disclosure during the consent process risks leaving the impression that compensation will cover only research infrastructure costs, while many of these arrangements allow for a variety of potential secondary

gains. Recent attempts to create more detailed disclosure guidelines of COIs for clinical research studies have been published,[23,24] but the extent of their implementation is unknown.

While many authors have recommended comprehensive and standardized disclosure of investigator relationships with industry, questions about where in the consent process such information is most effectively presented and whether potential subjects are able to understand the implications of these disclosures also need further study.[12,19]

Avoidance or minimization of potential COIs is the ultimate goal. An important step toward this goal is standardizing and making transparent current physician-industry relationships in ISCTs.[1,25,26] Development of disclosure practices for physicians in MS research may provide a model for COI disclosure in ISCT more broadly.

Conflict of interest

This study was not industry sponsored.

Andrew J Solomon received a research grant from the National Multiple Sclerosis Society and was a primary investigator in a multicenter clinical trial for a medication sponsored by Biogen Idec.

Eran P Klein has received honoraria for speaking at academic conferences and receives royalty payments for *The Birth of Bioethics* (Georgetown University Press, 2003).

John R Corboy reports that within the last year he was a primary investigator in a multicenter clinical trial for a medication sponsored by Novartis, Sun Pharma, Celgene Therapeutics, the National Multiple Sclerosis Society, and the National Institutes of Health. He has received research grants from the Juvenile Diabetes Research Foundation, the National Multiple Sclerosis Society, and Diogenix. He has served as a consultant for Novartis, Celgene Therapeutics, Teva Neurosciences, and Biogen Idec. He has received honoraria for speaking engagements from Pro CE, Rocky Mountain MS Center, via Genzyme, and for Grand Rounds at multiple academic institutions. He has been compensated for medical-legal work, as an Editor for *Neurology: Clinical Practice*, and is an uncompensated board member, NMSS Colorado-Wyoming Chapter.

James L Bernat serves on the editorial boards of *Neurocritical Care, Neurology Today*, and *Multiple Sclerosis and Related Disorders* (all unpaid) and the *Physician's Index for Ethics in Medicine* (paid). He receives royalty payments for *Ethical and Legal Issues in Neurology* (Elsevier, 2013), *Ethical Issues in Neurology* 3rd ed (Lippincott Williams & Wilkins, 2008), and *Palliative Care in Neurology* (Oxford University Press, 2004).

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Ross JS, Gross CP and Krumholz HM. Promoting transparency in pharmaceutical industry-sponsored research. *Am J Public Health* 2012; 102: 72–80.
2. Norris SL, Holmer HK, Ogden LA, et al. Conflict of interest disclosures for clinical practice guidelines in the national guideline clearinghouse. *PloS one* 2012; 7: e47343.
3. Holloway RG, Mooney CJ, Getchius TS, et al. Invited article: Conflicts of interest for authors of American Academy of Neurology clinical practice guidelines. *Neurology* 2008; 71: 57–63.
4. Thompson DF. Understanding financial conflicts of interest. *New Engl J Med* 1993; 329: 573–576.
5. GBI Research. *Multiple Sclerosis Therapeutics to 2019 – Treatment Diversification, Increasing Efficacy, and Pipeline Innovation Combine to Drive Growth*. July 2013. Bolton, UK: GBI. Available at: www.gbiresearch.com
6. IMS Institute for Health Informatics. *The Global Use of Medicines: Outlook Through 2016*. July 2012. NJ: IMS Inc. Available at: www.imshealth.com
7. Angelos P, Murphy TF, Sampson H, et al. Informed consent, capitation, and conflicts of interest in clinical trials: Views from the field. *Surgery* 2006; 140: 740–748.
8. Raftery J, Bryant J, Powell J, et al. Payment to healthcare professionals for patient recruitment to trials: Systematic review and qualitative study. *Health Technol Assess* 2008; 12: 1–128, iii.
9. Tosounidis TI and Kontakis GM. Clinical research: The patients' perspectives. *Injury* 2008; 39: 631–635.
10. Gray SW, Hlubocky FJ, Ratain MJ, et al. Attitudes toward research participation and investigator conflicts of interest among advanced cancer patients participating in early phase clinical trials. *J Clin Oncol* 2007; 25: 3488–3494.
11. Grady C, Horstmann E, Sussman JS, et al. The limits of disclosure: What research subjects want to know about investigator financial interests. *J Law Med Ethics* 2006; 34: 592–599, 481.
12. Weinfurt KP, Friedman JY, Allsbrook JS, et al. Views of potential research participants on financial conflicts

of interest: Barriers and opportunities for effective disclosure. *J Gen Intern Med* 2006; 21: 901–906.

13. Kim SY, Millard RW, Nisbet P, et al. Potential research participants' views regarding researcher and institutional financial conflicts of interest. *J Med Ethics* 2004; 30: 73–79.
14. Hall MA, Friedman JY, King NM, et al. Commentary: Per capita payments in clinical trials: reasonable costs versus bounty hunting. *Acad Med* 2010; 85: 1554–1556.
15. Shuchman M. Commercializing clinical trials — Risks and benefits of the CRO boom. *New Engl J Med* 2007; 357: 1365–1368.
16. Fisher JA and Kalbaugh CA. United States private-sector physicians and pharmaceutical contract research: a qualitative study. *PLoS medicine* 2012; 9: e1001271.
17. Weinfurt KP, Hall MA, Hardy NC, et al. Oversight of financial conflicts of interest in commercially sponsored research in academic and nonacademic settings. *J Gen Intern Med* 2010; 25: 460–464.
18. Fisher JA. Practicing research ethics: private-sector physicians & pharmaceutical clinical trials. *Soc Sci Med* 2008; 66: 2495–2505.
19. Licurse A, Barber E, Joffe S, et al. The impact of disclosing financial ties in research and clinical care: a systematic review. *Arch Intern Med* 2010; 170: 675–682.
20. Weinfurt KP, Hall MA, Dinan MA, et al. Effects of disclosing financial interests on attitudes toward clinical research. *J Gen Intern Med* 2008; 23: 860–866.
21. Hampson LA, Agrawal M, Joffe S, et al. Patients' views on financial conflicts of interest in cancer research trials. *New Engl J Med* 2006; 355: 2330–2337.
22. Raftery J, Kerr C, Hawker S, et al. Paying clinicians to join clinical trials: a review of guidelines and interview study of trialists. *Trials* 2009; 10: 15.
23. Rochon PA, Hoey J, Chan AW, et al. Financial conflicts of interest checklist 2010 for clinical research studies. *Open Med* 2010; 4: e69–91.
24. Weinfurt KP, Hall MA, King NM, et al. Disclosure of financial relationships to participants in clinical research. *New Engl J Med* 2009; 361: 916–921.
25. Ferris LE and Naylor CD. Physician remuneration in industry-sponsored clinical trials: the case for standardized clinical trial budgets. *Can Med Assoc J* 2004; 171: 883–886.
26. Morin K, Rakatansky H, Riddick FA, Jr, et al. Managing conflicts of interest in the conduct of clinical trials. *JAMA* 2002; 287: 78–84.

11.4 Industry Support of Medical Research: Important Opportunity or Treacherous Pitfall?

William M. Tierney, Eric M. Meslin, and Kurt Kroenke

Tierney, W, Meslin, E, Kroenke, K. Industry support of medical research: Important opportunity or treacherous pitfall? *Journal of General Internal Medicine* 31(2), 228–233 (2015).

Figure 1 reproduced from The Anatomy of Medical Research: US and International Comparisons. *Journal of the American Medical Association*. 313 (2), 2015. With permission from the American Medical Association.

JGIM

PERSPECTIVE

Industry Support of Medical Research: Important Opportunity or Treacherous Pitfall?

William M. Tierney, MD[1,2], Eric M. Meslin, PhD[2,3], and Kurt Kroenke, MD[1,2,4]

[1]Regenstrief Institute, Inc., Indianapolis, IN, USA; [2]Indiana University School of Medicine, Indianapolis, IN, USA; [3]Indiana University Center for Bioethics, Indianapolis, IN, USA; [4]Roudebush VA Center for Health Information and Communication, Indianapolis, IN, USA.

Pharmaceutical and device manufacturers fund more than half of the medical research in the U.S. Research funding by for-profit companies has increased over the past 20 years, while federal funding has declined. Research funding from for-profit medical companies is seen as tainted by many academicians because of potential biases and prior misbehavior by both investigators and companies. Yet NIH is encouraging partnerships between the public and private sectors to enhance scientific discovery. There are instances, such as methods for improving drug adherence and post-marketing drug surveillance, where the interests of academician researchers and industry could be aligned. We provide examples of ethically performed industry-funded research and a set of principles and benchmarks for ethically credible academic–industry partnerships that could allow academic researchers, for-profit companies, and the public to benefit.

KEY WORDS: ethics, research; conflict of interest; public–private partnerships; research support.
J Gen Intern Med 31(2):228–33
DOI: 10.1007/s11606-015-3495-z

Federal funding of research has decreased over the past decade.[1] At the same time, NIH has called for more collaboration between industry and academic investigators. For example, NIH's *Discovering New Therapeutic Uses for Existing Molecules* initiative will test more than 20 compounds from industry partners for their effectiveness against a variety of diseases and conditions.[2] *Accelerating Medicine Partnerships* is a collaboration among NIH, ten pharmaceutical companies, and non-profit patient advocacy organizations to identify and validate the most promising biological targets of disease for new diagnostic and drug development.[3] "Clearly, we need to speed the pace at which we are turning discoveries into better health outcomes," said NIH Director Collins. "NIH looks forward to working with our partners in industry and academia to tackle an urgent need that is beyond the scope of any one organization or sector".[4] Additionally, since passage of the Patent and Trademark Law Amendments ("Bayh–Dole") Act of 1980,[5] many academic institutions encourage faculty to patent and commercialize their discoveries, leading to mutually—scientifically and financially—beneficial partnerships between universities, their individual scientists, and private sector companies. In the wake of this engagement between academia and industry, and the enhanced scrutiny of industry payments to physicians prompted by passage of the Physician Payment Sunshine Act,[6] universities nationwide are revising their guidelines for conducting research and managing conflicts of interest.

Industry and government together have consistently funded most medical research in the U.S. (Fig. 1). Notably, industry dominates: research funding by industry in 2012 was $68 billion compared to $38 billion from federal agencies. Moreover, between 1994 and 2012, industry funding of medical research grew by 147 %, compared with 48 % for federal agencies, which was less than the 57 % inflation during those years.[7] The goal of federal research funding is to generate new knowledge that will enhance health and health care. The goal of research funding by for-profit companies is maximizing income to their shareholders. Increased knowledge and enhanced care, if they happen at all, are byproducts of the profit motive.

Can academicians' interest and industry's needs be aligned? For example, a company developing a new drug that may have fewer side effects might be interested in funding research into the incidence of adverse effects from currently marketed drugs. An academic researcher might have a strong interest in elucidating the adverse effect profile of that class of drugs when used in everyday settings among patients who are usually, if not always, excluded from pre-marketing studies.[8] Studies of how drugs and devices are used in everyday practice and the outcomes of treatment should be of mutual interest and benefit to both academic researchers and industry. For example, Bristol-Myers Squibb was about to launch a new antipsychotic drug and contracted with one of us (WMT) to conduct a study of the incidence of weight gain and diabetes among patients taking any of the currently available antipsychotics; the results were published in *JGIM*.[9]

Both academia and industry have interests in post-marketing drug surveillance.[10] The FDA requires companies to conduct post-marketing surveillance (phase IV studies) of new drugs and certain devices. Whereas academic

Received July 2, 2015
Revised July 16, 2015
Accepted July 23, 2015
Published online August 26, 2015

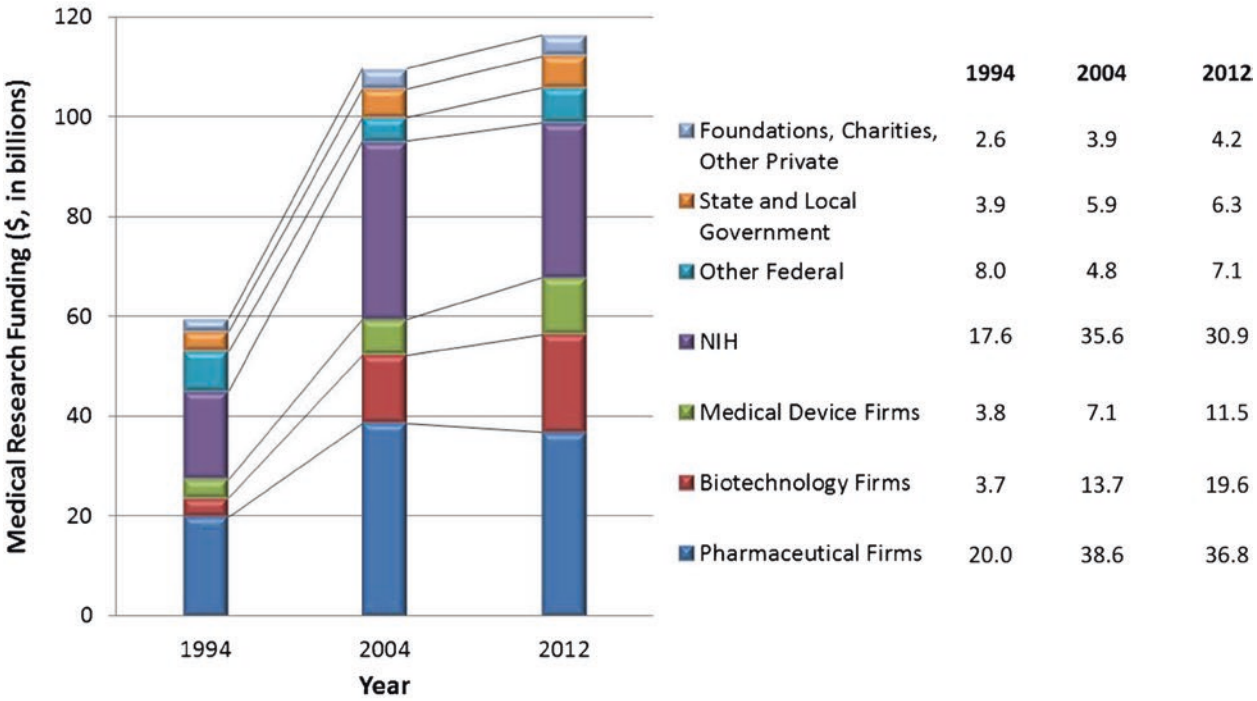

Fig. 1 Growth in medical research funding by source from 1994 to 2012 ($, in billions)[1]

investigators are interested in true estimates of benefits and risks of new treatments, for-profit drug and device companies would want to report great benefits and low risks. We believe that academic researchers are more likely to perform unbiased post-marketing studies than either researchers employed by the company marketing the drug in question or for-profit research companies whose livelihood depends on satisfying their customers.

Academic researchers and industry scientists can also share interests in generating knowledge relevant to patient care. For example, clinicians hope and expect patients to take the medications they prescribe, and pharmaceutical companies benefit when patients take them. Thus both clinician-investigators and pharmaceutical companies have obvious interests in drug adherence and in developing and validating methods for assessing and improving adherence. Industry and academic investigators can also have mutual interests in improving our ability to identify, assess, and manage important patient outcomes. For example, the Regenstrief Institute has a five-year contract with Merck Sharp & Dohme to develop and conduct mutually interesting and beneficial research projects.[11] Researchers from the Regenstrief Institute and Indiana University and scientists from Merck propose collaborative one-year projects. A review committee comprising three senior investigators from both IU/Regenstrief and Merck reviews the proposals, eliminates some, and ranks the rest. Merck decides on its allocation to the collaboration each year, and then the review committee begins at the top of the rank list and funds projects until all allocated funds are expended. Publication of study results in peer-reviewed journals is a required deliverable of each project. Table 1 shows projects funded in the first four years of this collaboration. Importantly, like federally funded projects, the grants reimburse the salaries of IU/Regenstrief investigators and professional staff. No bonuses or extra payments are made.

Industry-funded research has a risk of bias and misconduct that can mislead readers,[12–14] consequently causing pain, suffering, and sometimes death.[15] Neither academia nor the private sector is immune from ethical scrutiny or responsibility, though public perception rarely gives high marks to the pharmaceutical industry's ethical behavior.[16] The key is minimizing bias through rigorous studies devised, conducted, and reported by academic investigators whose income is not tied to the drug being evaluated. Each of these—research methods, how they are applied, and how results are reported—is a source of bias, regardless of funding source, that rigor and vigilance can minimize in order to generate new knowledge and patient benefit.

For example, Kroenke and his colleagues received funding from Pfizer to develop screening instruments for depression (the PHQ-9) and anxiety (the GAD-7).[17] Both have become standard screening tools. The *JGIM* original article validating the PHQ-9[18] has been cited more than 3500 times, according to Web of Science[19]; it is *JGIM's* most highly cited article ever. Whereas both the PHQ-9 and GAD-7 are open-source and free to use, some survey instruments developed with federal funding require license fees,[20] an unfortunate trend where

Table 1 Funding of Projects in the First Four Years of the Regenstrief-Merck Collaboration

Project title	Brief description of project goals
Project 1: Leveraging Regenstrief's electronic medical record (EMR) and capabilities to enhance subject recruiting	Test the ability of a new identification system for EMR-enabled identification and recruitment of patients into clinical trials.
Project 2: Regenstrief-Merck Scholar's Award in Pharmacoepidemiology and Informatics	Create two annual visiting scholar positions whose focus will be primarily on the link between pharmacoepidemiology and biomedical informatics, leveraging big data analytics to: (1) improve patient care, (2) obtain better patient outcomes, and (3) lower costs.
Project 3: Building a phenotype library using Regenstrief's EMR	Define and validate a set of three algorithms for defining phenotypes of interest, validating them against human interpretation of medical charts.
Project 4a: Medication adherence in type 2 diabetes	Determine the patterns of use for medications prescribed to patients with type 2 diabetes mellitus, targeting medications for diabetes and associated metabolic disorders. Determine what patient-centered interview data might be collected, evaluate the merits of electronic monitoring of medications, and plan an intervention to improve adherence to medications. (This project was terminated due to feasibility issues.)
Project 4b: Medication adherence in respiratory disorders	Test whether monitoring asthma medication adherence using prescription records and providing feedback to patients can improve drug adherence and asthma control among patients non-adherent to their inhaled controller medications.
Project 5: Computerized reminders to promote medication adherence and utilization	Support more consistent and effective use of prescribed medications by identifying optimal physician and patient-directed strategies to improve appropriate medication adherence and utilization.
Project 6a: Usage, Benefits, and Adverse Effects of Loop Diuretics in Patients with Heart Failure or Hypertension	Identify and describe the characteristics of patients with diagnosed hypertension and heart failure using EMR data, and use prescription records to assess adherence for heart failure and hypertension medications, and relate clinical outcomes to medications prescribed and adherence.
Project 6b: Longitudinal Modeling of Heart Failure Progression	Utilize longitudinal EMR data to characterize the changes in ejection fraction and/or New York Heart Association chronic heart failure classification. Examine the impact of patient-specific covariates (drug treatment, intensity, age, weight, sex, etc.) on the rate of heart failure progression.
Project 7: Sensitivity analysis of Mini-Sentinel's protocol of active surveillance of acute myocardial infarction in association with antidiabetic agents	Better understand the sensitivity of risk estimates with respect to a set of parameters associated with design decisions. To accomplish this, the project evaluated a protocol from the Mini-Sentinel for the Active Surveillance of Acute Myocardial Infarction in Association with Use of Anti-Diabetic Agents.
Project 8: OpenMRS–Merck Strategic Collaboration	Integrate a Merck business analyst and developer into the OpenMRS community who can comprehend and assist with open-source EMR development.
Project 9: Calibrating evidence of drug risk by estimating clinical database bias	Develop methods to adjust results for more accurate answers to drug outcome research questions within the Indiana Network for Patient Care (INPC). Develop "database fingerprinting" methods that can be applied to any database in the Observational Medical Outcomes Partnership (OMOP) common data model format.
Project 10: Predictive modeling of drug–outcome associations	Develop and compare optimal predictive modeling techniques for identifying patients at risk of known drug outcomes.
Project 11: Chronic kidney disease and resistant hypertension	Define the rates of resistant hypertension in populations with and without chronic kidney disease.
Project 12: Collecting and incorporating patient-reported data into a medication adherence decision support system	Determine whether non-interruptive claims-based adherence alerts enhanced with patient-reported data and tailored recommendations can increase the number of conversations clinicians and patients have about their adherence to oral medications for diabetes. (Due to delays encountered during development and deployment, this project was discontinued.)
Project 13: Development and feasibility of a medication adherence protocol for older adults with mild cognitive impairment	Identify and quantify barriers to medication adherence in older adults with mild cognitive impairment.
Project 14: Investigation of physician reminders and recommendation scripts for HPV vaccination	Evaluate the effect of automated physician-targeted reminders and recommended scripts on first dose uptake of HPV vaccine and rates of return for second dose.
Project 15: EMR-based detection and display of hypoglycemic risk in diabetic patients	Develop a predictive model of hypoglycemia risk in patients taking insulin or sulfonylureas. Design an alert that will be delivered to providers accessing high-risk patients' EMRs.
Project 16: Melanoma algorithm development and validation	Determine the sensitivity and positive predictive value of defining melanoma in the INPC database using EMR data and data derived from natural language processing (NLP).
Project 17: Medication adherence in order adults with cognitive impairment (continuation of Project 13)	Identify and quantify barriers to adherence in older adults with mild cognitive impairment.
Osteoporosis Center of Excellence (OCOE)-1: Sub-Optimal Outcomes of Bisphosphonates Treatment in the Real World	Examine the prevalence and healthcare burden of osteoporosis patients who sustain fractures, lose bone mineral density, or remain osteoporotic despite being adherent to bisphosphonates treatment.
OCOE-2: Renal Impairment in Osteoporosis	Quantify the unmet medical need in the area of comorbid osteoporosis and chronic kidney disease, as current osteoporosis therapies are not recommended in patients with moderate to severe chronic kidney disease.
OCOE-3: Finding fractures and other phenotypes of high interest using EMR data and NLP	Develop and validate coding algorithms for fractures and other phenotypes to enhance observational studies.
OCOE-4: Broadening osteoporosis-related data in the INPC	Enhance researchers' ability to use the INPC for osteoporosis-related studies by creating the nation's largest repository of structured bone mineral density scans linked to EMR data.

(*continued on next page*)

Table 1. (continued)

Project title	Brief description of project goals
OCOE-5: High-volume osteoporosis and patient access registry project	Establish a large consenting cohort of patients (with links to their EMRs) for rapid recruitment for future osteoporosis-related studies.
OCOE-6: Disparities in osteoporosis treatment	Use patient and provider characteristics in multivariate models to predict which patients with osteoporosis, low bone mineral density, or fractures receive treatment with bisphosphonates or other osteoporosis drugs.
OCOE-7: Improving the capture, interpretation and use of DXA data	Upload DXA data from selected health systems' radiology departments and local clinics into INPC and assess the variability of longitudinal bone mineral density measurements in the clinical setting.
OCOE-8: Diagnosis of atypical subtrochanteric fractures in the clinical setting	Estimate the proportion of atypical femur shaft fractures in women with non-traumatic femur fractures, and identify clinical factors predicting atypical femur shaft fractures.
Cross-Collaboration Initiative (CCI) -1: Regenstrief-Merck Scholar's Award in Pharmacoepidemiology and Informatics	Create the first-ever combined pharmacoepidemiology-medical informatics fellowship to develop and train world-class leaders at the intersection of big data, pharmaceutical research, and health information technology.
CCI-2: Regenstrief Boot Camp	Hold an intensive two-day training seminar that will provide Merck and local non-Regenstrief investigators knowledge of the wide-ranging resources and capabilities available at the Regenstrief Institute.
CCI-3: EMR Summit	Hold a summit of commercial EHR and health IT developers to promote awareness and adoption of innovations in evidence-based care, patient safety, and user experience design.
CCI-4: Natural Language Processing Core	Expand Regenstrief's and Merck's capabilities to glean information from text data in support of current and future projects.
CCI-t: Electronic patient reported outcomes (ePRO) capture platform	Create a flexible, scalable, and generalizable electronic platform for generating and storing patient-reported outcomes on an unlimited variety of topics.

Total Projects = 32
Manuscripts: 14 submitted, 5 published or accepted for publication to date
29 Presentations at scientific meetings and conferences to date

patient-reported measures are frequently proprietary rather than in the public domain.[21]

Certainly there are well-documented cases where industry-funded research has been biased. For example, two systematic reviews found that studies sponsored by industry reported significantly greater benefits and less harm than studies with other sources of funding.[22,23] Similarly, there are well-known examples where industry has squelched (or attempted to squelch) study results that were unfavorable to their products.[24,25] Pharmaceutical companies have also paid ghostwriters to draft reviews of drug treatment favorable to their products, and then sought academicians to "author" the articles, with the goal of biasing the medical literature.[26] But does such obviously unethical behavior by some investigators and companies mean that industry-funded research can never be conducted by academic scientists without the results being questioned? We argue that academic–industry relationships can be "ethically credible," meaning that specific ethical principles are followed that minimize the risk that industry funding will bias the planning, conduct, or reporting of studies. Indeed, academic–industry relationships are not only possible, they are desirable as a means to maximize discoveries and patient benefits as federal research dollars are dwindling.

An example of an ethically credible partnership was the ARTIST study that was funded by Eli Lilly to assess the effects of different selective serotonin reuptake inhibitors (SSRIs) on depression and other outcomes in primary care.[27] The sponsor had postulated that its SSRI (fluoxetine) would be more effective than two competing SSRIs (sertraline and paroxetine). However, the study found no differences among the three SSRIs as reported in a high-impact journal (*JAMA*), despite not favoring the sponsor's drug. Indeed, the evidence supporting "funding bias" has recently been questioned by social scientists as well as the Cochrane collaboration.[28,29]

To counter potential bias due to industry funding of research, the Regenstrief Institute commissioned one of us (EMM) and his colleagues at the Indiana University Center for Bioethics (IUCB) to review Regenstrief's collaboration with Merck.[11] Reviews of this kind are rare, but have been reported elsewhere.[30] During the second year of the five-year collaboration, IUCB faculty and staff reviewed the contract between Regenstrief and Merck, assessed the bioethics literature concerning industry-funded research, surveyed Indiana University/Regenstrief investigators and staff engaged in one or more Merck-funded activities, and developed a set of principles and benchmarks for ethically credible academic–industry partnerships (Table 2). IUCB reviewers found the Regenstrief-Merck collaboration to be ethically conducted overall, but that it could be improved, especially in communicating the collaboration's policies and operating principles to all faculty and staff participants.[31] The policies and procedures governing the Regenstrief-Merck collaboration were deemed to address the key ethical issues. Several benchmarks were not fully met, and the report made specific recommendations that the collaboration's leaders followed. In subsequent years, the collaboration has met all benchmarks. Specific recommendations followed were to 1) increase transparency and enhance trust by more fully educating all investigators and staff on the collaboration's policies and procedures; 2) broadcast the processes for ranking projects and selecting those to be funded; 3)

Table 2 Principles and Benchmarks for Ethically Credible Academic–Industry Partnerships

Principle	Benchmark
Academic freedom	1. Promote investigator-initiated science and protect the ability to attract and maintain federal research support 2. Permit investigators to initiate or continue collaboration with any other qualified group, person or entity 3. Ensure that all investigators involved in the partnership are given equal opportunity to submit proposals for funding 4. Avoid obligating faculty to work outside their own self-defined scientific area
Conflict of interest policy and management	5. Protect students, fellows and post-doctoral fellows involved in collaborative projects from exploitation 6. Ensure that effective mechanisms exist to eliminate, control or manage conflicts of interest in the partnership
Intellectual property	7. Ensure that all investigators and both partners retain their proprietary and intellectual property rights throughout and after the partnership
Data-sharing, access	8. Ensure that data-sharing arrangements are explicit and that all rights to access data are fairly negotiated at the outset of the partnership
Effective governance	9. Establish parameters for what type of projects will and will not be funded (e.g., add-on projects, training, pilot studies) 10. Create ways to protect each party from an unexpected end to the partnership 11. Formally assess the efficiency, effectiveness and achievements of the partnership on an annual basis 12. Ensure that clear, comprehensive and efficient procedures exist for all governance entities of the partnership and are known to all investigators
Protection of human subjects	13. Ensure that all investigators, staff and other participants in the partnership have adequate training in the responsible conduct of research and related ethical issues 14. Ensure that all projects in the partnership aim to satisfy the highest ethical standards
Publication	15. Ensure the right of all researchers associated with the partnership to publish 16. Disseminate all research results at the conclusion of collaborative studies in a timely fashion 17. Ensure that authorship follows ICMJE guidelines
Social, scientific and industrial value	18. Maintain competitive advantage in the specified research domains 19. Structure the research to maximize potential benefit for communities and society 20. Structure the partnership to have the best chance of benefiting both partners and harming neither
Transparency	21. Widely publicize the partnership agreement and collaborative opportunities to the public and employees 22. Establish procedures for frequent and effective communication between partners 23. Ensure that both partners are aware of other partnerships each may be involved in

include a wider range of Institute and university investigators in the invitation to propose studies; 4) publicize the collaboration's distinctive conflict of interest policies; and 5) proactively assess investigators' concerns about the collaboration and provide investigators with more opportunities to learn about the collaboration and provide input.

As a result of the IUBC evaluation and the more than two decades of research collaboration with industry, the Regenstrief Institute has launched an Industry Research Office (IndRO) that facilitates conversations with prospective industry funders, identifies Regenstrief and other university principle investigators and co-investigators, helps design protocols and write proposals, manages communication and contracts, and follows the principles and benchmarks for a wider range of investigators, funders, and studies. The overriding goal of the IndRO is to provide academic researchers with alternative sources of funding their research as federal sources become increasingly constrained. In addition to faculty and staff salaries for performing research, funds from industry-sponsored studies support IndRO's management infrastructure, local clinical data repositories, and other research resources. To maintain the studies' intellectual independence and scholarly focus, all industry contracts contain a clause giving the investigators the right to publish any and all study results, and an article submitted to a peer-reviewed journal is the final required deliverable of all contracts.

The moral outrage engendered by past misbehavior on the part of the drug and device industry and academic researchers can affect all financial relationships between medical schools and industry.[32,33] If stringent ethical guidelines are followed, private sector companies can be an important source of funding for ethical, high-quality, important academic research. Universities must develop and implement policies and procedures to maximize the effectiveness and ethical conduct of all research, regardless of funding source. We are confident that this is possible and that industry, academic medical scientists, and the patients and communities they serve can all benefit.

Conflict of Interest: *Dr. Tierney has received research funding from Merck Sharp & Dohme, Eli Lilly, Bristol-Myers Squibb, GlaxoSmithKline, Caremark, and Integrated Disease Management, Inc. He has never owned stock in individual medically related companies and has never received honoraria, speaking fees, or personal income from any medically related company. He is the President and CEO of the Regenstrief Institute, Inc., which has an Industry Research Office that facilitates research contracting between academic investigators and the private sector. All residual funds realized by this research support Regenstrief's local research infrastructure. No funds result in bonuses or additional income to investigators or staff.*

Dr. Meslin does not now but has previously received consulting fees from Eli Lilly. He sits on the Science and Industry Advisory Committee of Genome Canada, for which he receives an annual honorarium.

Dr. Kroenke has received research funding from Eli Lilly, Pfizer, and Wyeth. He does not now but has previously received consulting fees and/or honoraria from Eli Lilly, Wyeth, Forest Laboratories, and Bristol-Myers Squibb. He has no investments in individual for-profit companies.

Corresponding Author: *William M. Tierney, MD; Regenstrief Institute, Inc., 410 West Tenth Street Suite HS2000, Indianapolis, IN 46202, USA (e-mail: wtierney@regenstrief.org).*

REFERENCES

1. **Moses H III, Matheson DHM, Cairns-Smith S, George BP, Palisch C, Dorsey R.** The anatomy of medical research: US and international comparisons. JAMA. 2015;313:174–89.
2. National Center for Advancing Translational Sciences. Discovering new therapeutic uses for existing molecules. Available at: http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html. Accessed April 25, 2015.
3. National Institutes of Health. Accelerating medicines partnerships. Available at: http://www.nih.gov/science/amp/index.htm. Accessed April 25, 2015.
4. National Institutes of Health. NIH launches collaborative program with industry and researchers to spur therapeutic development. Available at: http://www.nih.gov/news/health/may2012/od-03.htm. Accessed April 25, 2015.
5. Patent and Trademark Law Amendments Act of 1980, Pub. L. No. 96–517, 94 Stat. 3015, 69331 (1980) (codified as amended at 35 U.S.C. ch. 30 (2011)).
6. Patient Protection and Affordable Care Act, Pub. L. No. 111–148, 124 Stat. 119 (2010); Sec. 6002: Transparency Reports and Reporting of Physician Ownership or Investment Interests (codified as 42 U.S.C.A. § 1320a-7h).
7. USInflation.org. US inflation rate calculator. Available at: http://usinflation.org/us-inflation-rate-calculator/. Accessed July 7, 2015.
8. **Singh S, Loke YK.** Drug safety assessment in clinical trials: methodological challenges and opportunities. Trials. 2012;13:138.
9. **Farwell WR, Stump TE, Wang J, Tafesse E, L'Italien G, Tierney WM.** Weight gain and new onset diabetes associated with olanzapine and risperidone. J Gen Intern Med. 2004;19:1200–5.
10. **Psaty BM, Meslin EM, Breckenridge A.** A lifecycle approach to the evaluation of FDA approval methods and actions: opportunities provided by a new IOM report. JAMA. 2012;307(23):2491–2.
11. **Jain SH, Rosenblatt M, Duke J.** Is big data the new frontier for academic-industry collaboration? JAMA. 2014;311:2171–2.
12. **Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B.** Evidence b(i)ased medicine–selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. BMJ. 2003;326:1171–3.
13. **Godlee F, Smith J, Marcovitch H.** Wakefield's article linking MR vaccine and autism was fraudulent. BMJ. 2011;342:c7452.
14. **Cyranoski D.** Research integrity: cell-induced stress. Nature. 2014;511(7508):140–3.
15. **Hollon T.** Researchers and regulators reflect on first gene therapy death. Nat Med. 2000;6:6.
16. **Olsen AK, Whalen MD.** Public perceptions of the pharmaceutical industry and drug safety: implications for the pharmacovigilance professional and the culture of safety. Drug Saf. 2009;32:805–10.
17. **Kroenke K, Spitzer RL, Williams JBW, Löwe B.** The Patient Health Questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. Gen Hosp Psychiatry. 2010;32:345–59.
18. **Kroenke K, Spitzer RL, Williams JBW.** The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606–13.
19. Web of Science. Available at: www.isiknowledge.com. Accessed April 25, 2015.
20. **McHorney CA, Ware JE Jr, Raczek AE.** The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993;31:247–63.
21. **Newman JC, Feldman R.** Copyright and open access at the bedside. N Engl J Med. 2011;365(26):2447–9.
22. **Song F, Parekh S, Hooper L, et al.** Dissemination and publication of research findings: an updated review of related biases. Health Technol Assess 2010;14:iii. ix-xi, 1–193.
23. **Bero L.** Industry sponsorship and research outcome: a Cochrane review. JAMA Intern Med. 2013;173:580–1.
24. **Rennie D.** Thyroid storm. JAMA. 1997;277:1238–43.
25. **Blumenthal D, Campbell EG, Anderson MS, Causino N, Louis KS.** Withholding research results by academic life scientists: evidence from a national survey of faculty. JAMA. 1997;277:1224–8.
26. **Tierney WM, Gerrity MS.** Scientific discourse, corporate ghostwriting, journal policy, and public trust. J Gen Intern Med. 2005;20:550–1.
27. **Kroenke K, West SL, Swindle R, et al.** Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care: a randomized trial. JAMA. 2001;286:2947–55.
28. **Krimsky S.** Do financial conflicts of interest bias research? An inquiry into the "funding effect" hypothesis. Sci Technol Hum Values. 2013;38:566–87.
29. **Sterne JA.** Why the Cochrane risk of bias tool should not include funding source as a standard item. Cochrane Database Syst Rev. 2013;12:ED000076.
30. **Carpenter WT Jr, Koenig JI, Bilbe G, Bischoff S.** At issue: a model for academic/industry collaboration. Schizophr Bull. 2004;30:997–1004.
31. **Meslin EM, Gaffney MM, Quaid KA, Schwartz PH, Pitt AR, Rager JB.** Final summary report: Review of the Merck-Regenstrief partnership. Available at: http://hdl.handle.net/1805/6044. Accessed July 7, 2015.
32. **Rosenbaum L.** Beyond moral outrage – Weighing trade-offs of COI regulation. N Engl J Med. 2015;372:2064–8.
33. **Steinbrook R, Kassirer JP, Angell M.** Justifying conflicts of interest in medical journals: a very bad idea. BMJ. 2015;350:h2942.

References

Campbell E, Bogeli C, Rao S, Abraham M, Pierson R, Applebaum S. Industry relationships among academic institutional review board members; changes from 2005 through 2014. JAMA Intern Med. 2015;175(9):1500–6.

Dunn A, Colera E, Mandl K, Bourgeois F. Conflict of interest disclosure in biomedical research: a review of current practices, biases, and the role of public registries in improving transparency. Res Integr Peer Rev. 2016;1:1.

Elliott C. Institutional pathology and the death of Dan Markingson. Account Res. 2016. Epub ahead of print.

Kearns C, Glantz S, Schmidt L. Sugar industry influence on the scientific agenda of the National Institute of Dental Research's 1971 National Caries Program: a historical analysis of internal documents. PLoS Med. 2015;12(3):e1001798.

Resnik D. Institutional conflicts of interest policies at U.S. academic research institutions. Acad Med. 2016;91(2):242–6.

Wilson J. Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency. Mol Genet Metab. 2009;96:151–7.

Additional Suggested Reading

Dunn A, Colera E, Mandl K, Bourgeois F. Conflict of interest disclosure in biomedical research: a review of current practices, biases, and the role of public registries in improving transparency. Res Integr Peer Rev. 2016;1:1. (*A public registry of competing interests is needed in order to have a comprehensive view of COI.*)

Elliott C. Institutional pathology and the death of Dan Markingson. Account Res. 2016. Epub ahead of print. (*Apparent institutional regulatory oversight failure by a major public university is described*. 2017 24(2):65–79)

Resnik D. Institutional conflicts of interest policies at U.S. academic research institutions. Acad Med. 2016;91(2):242–246. (*Policy development for institutional conflicts of interest are incomplete.)*

Yanagawa H. Current regulatory systems for clinical trials in Japan: Still room for improvement. Clin Res Regul Aff. 2014;31(2–4):23–28. (*Describes how a country develops its research regulatory system including management of COI.*)