

Curbing Industry Sponsors' Incentive to Design Post-Approval Trials that are Suboptimal for Informing Prescribers but More Likely than Optimal Designs to Yield Favorable Results

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ABSTRACT

Many studies have shown that commercially-sponsored clinical trials are more likely than publicly-financed trials to produce results that are favorable to the sponsoring firm. There is no research, however, to support the allegation that industry sponsors intentionally design methodologically inferior studies. Rather than empirically determining whether commercially financed research is less sound than its publicly supported counterpart, this Article focuses on the financial incentives created by the current regulatory climate. This Article demonstrates that pharmaceutical companies are being put to a cruel choice between optimally advancing the medical literature and honoring their fiduciary duties to shareholders by designing suboptimal phase IV protocols. As pharmaceutical companies have little incentive to design suboptimal protocols for other types of trials, this Article focuses exclusively on non-required post-marketing studies not intended to support supplemental NDA labeling changes. After arguing that the present regime is incapable of reining in conflicted sponsors, this Article offers a solution that has the potential to align industry interests with the public health.

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I. INTRODUCTION

Studies have shown that commercially-funded clinical trials are more likely than publicly-financed trials to produce results that are favorable to the sponsoring firm. This Article investigates one possible reason for the disparate outcomes—the theory that industry sponsors intentionally design methodologically inferior trials. Rather than empirically determining whether commercially financed research is less sound than its publicly supported counterpart, this paper focuses on the financial incentives created by the current regulatory climate. This Article purports to demonstrate that pharmaceutical companies are being put to a cruel choice between optimally advancing the medical literature and honoring their fiduciary duties to shareholders by designing suboptimal phase IV protocols. As pharmaceutical companies have little incentive to design suboptimal protocols for other types of trials, *this Article focuses exclusively on non-required post-marketing studies not intended to support supplemental NDA labeling changes* (hereinafter referred to as “voluntary, non-label-seeking, post-approval studies”). After arguing that the present regime is incapable of reining in conflicted sponsors, it offers a solution that has the potential to align industry interests with the public health.

Part II of the Article demonstrates that if commercial sponsors are intentionally designing suboptimal trials, the proper response is not to rebuke the companies, but rather to reconfigure the system to provide firms with a financial incentive to conduct such research. This Article relies on findings from the social psychology literature to explain other authors’ tendencies to harshly reprimand pharmaceutical companies, and stipulates that this Article avoids such demonization by focusing on the situational influences that sculpt industry action.¹

Part III begins by introducing the research that shows that industry-funded trials are more likely than taxpayer-financed trials to produce positive data. After discussing commercial sponsors’ increasing ability to exercise control over the design of clinical trials during the last two decades, it questions previous findings that suggest that private research is at least as methodologically sound as publicly-funded research. Part III then articulates the myriad ways in which pharmaceutical companies may have an incentive to design trials that

¹ “Demonization” is a word used by Arthur Caplan to depict authors’ tendency to staunchly criticize pharmaceutical companies. See, e.g., Arthur L. Caplan, *Indicting Big Pharma*, 93 AM. SCIENTIST 68, 68 (2005).

are suboptimally informative to the medical community but more likely than the optimal designs to yield favorable results. For example, industry sponsors may feel financial pressure to inappropriately measure surrogate outcomes or run a study that is too short to adequately determine whether the drug in question is safer than a competitor's product. Finally, Part III offers suggestions for future research that could empirically determine whether pharmaceutical companies are indeed more likely than disinterested academics to design suboptimal phase IV trials.

Part IV begins by demonstrating that the FDA, physicians, insurance companies, journal editors, and the tort system are all incapable of eliminating the industry's incentive to design methodologically suboptimal trials. After discussing solutions proffered by other authors, Part IV argues that the interests of commercial sponsors and the public health could be aligned by (a) creating a federal body that disseminates comparative data on alternative therapies, and (b) restructuring the insurance system so that consumers have a financial incentive to seek out physicians and health plans that are not improperly influenced by methodologically suboptimal studies.

Finally, Part V offers a brief conclusion.

II. WHOSE FAULT IS IT?: A LESSON FROM STANLEY MILGRAM

A. *The Fundamental Attribution Error—A Brief Description*

The "fundamental attribution error" is a phrase used to describe the natural human tendency to only see disposition, even though situational forces are far more controlling.² When person A observes an action taken by person B, A automatically and unconsciously assumes that B acted as she did because of B's internal preferences. This premise is true notwithstanding the fact that B's action was hardly a choice at all, as exogenous pressures—rather than B's disposition—caused her to behave in that manner.³ The groundbreaking series of studies conducted by Yale psychologist Stanley Milgram presents the paradigmatic example of the fundamental attribution er-

² Jon Hanson & David Yosifon, *The Situation: An Introduction to the Situational Character, Critical Realism, Power Economics, and Deep Capture*, 152 U. PA. L. REV. 129, 136 (2003) [hereinafter Hanson & Yosifon, *The Situation*]; Jon Hanson & David Yosifon, *The Situational Character: A Critical Realist Perspective on the Human Animal*, 93 GEO. L.J. 1, 24–25 (2004) [hereinafter Hanson & Yosifon, *The Situational Character*].

³ The fundamental attribution error also speaks to the idea that internal cognitive biases tend to plague decision-making even though third party observers attribute human behavior to conscious, rational thought. This section, however, focuses on external situational pressure.

ror.⁴ The contribution of Milgram's studies to the understanding of human behavior has been elegantly described elsewhere by Hanson and Yosifon:

Milgram arranged an experimental situation in which subjects—compensated volunteers—were led to believe that they were participating in a study on memory. In the basic design of the experiment, the subject first met another “subject”—who was actually one of Milgram's confederates—and the two drew straws to determine what part in the experiment they would take. The confederate was inevitably assigned the role of the “student,” and promptly strapped into a chair with electrodes affixed to his body. The true subject was (seemingly randomly) assigned the role of the “teacher,” and was instructed to administer an electric shock—by flipping a switch on a shock box—each time the “student” incorrectly answered a question posed by the experimenter. The “teacher” was led to believe that the shocks would be painful, and that their intensity would increase in fifteen-volt increments with each wrong answer—from 15 volts all the way up to 450 volts, which was labeled “Danger! XXX!” on the shock box.

Before the experiment was undertaken, Milgram described the protocol to lay people and psychologists and then asked both groups to estimate how far most “teachers” would go with the shocking before refusing to continue. Those surveyed believed, as might the reader, that most would refuse early on. College students predicted that just 1 in 100 subjects would shock all the way to 450 volts, and professional psychologists predicted that only 1 in 1000—“the sadists”—would go that far.

....

In the basic design of the experiment, 100% of the subjects continued with the shocking at least to 350 volts, and 65% went all the way to 450 volts (“Danger! XXX!”). The dispositionist assumption, that people would never freely choose to knowingly inflict pain like that on an innocent subject in the absence of a highly salient situational force—such as a gun to their heads—is robust. But it is often wrong. In our dispositionism we fail to appreciate the powerful, but unseen, situational influences over the subjects' behavior in Milgram's lab. Milgram performed his study in numerous settings on hundreds of subjects who were, in all respects, typical people. They were not sadists; they were simply, like all of us, situational characters who were subject to unappreciated but profound influences in the situation. Indeed, Milgram was able to alter his subjects' behavior by altering the situational influences. By varying the proximity of the “teacher” to the “stu-

⁴ Hanson & Yosifon, *The Situation*, *supra* note 2, at 150–54.

dent,” or the “teacher” to the “experimenter,” or by altering the prestige of the experimental setting (by moving the location of the experiment from Yale to Bridgeport, Connecticut), Milgram discovered he could increase or decrease the level of shocking that subjects would be willing to administer.

Experiments like Milgram’s, and there are literally hundreds of others, have demonstrated that we place far too much emphasis on disposition—on an individual’s perceived motivations, preferences, choices, and will—in accounting for her conduct. In so doing we fail to appreciate the very potent, though often unnoticed, influences of situation.⁵

B. What the Fundamental Attribution Error Can Teach Us about Pharmaceutical Companies

Like the rest of us, modern day critics of the pharmaceutical industry are subject to the fundamental attribution error. Instead of critiquing the regulatory regime that shapes industry behavior, they condemn the companies as atrocious beings with bad intentions.⁶ Industry critics see drug companies not as corporate actors enmeshed within a complex regulatory framework, but rather as personified entities fulfilling internal preferences for profits. Katharine Greider’s book, entitled *The Big Fix: How the Pharmaceutical Industry Rips Off American Consumers*, concludes with the following line: “Like the childhood bully on the block, increasingly unpopular but seemingly invincible, maybe the drugmakers are really asking a desperate question: Who’s going to stop me?”⁷

Of course, just like the subjects in Milgram’s experiment who administered shocks all the way up to the line labeled “Danger! XXX!,” pharmaceutical companies (and their managers/directors) are not immoral beings who do not care about the public health. They are economic actors who behave according to a set of well-established market principles. The regulatory landscape imposed by the Food and Drug Administration, as well as state corporate law, shapes managerial decisions within firms. Although the law is in flux and open to debate, legal scholars generally agree that corporate managers owe a fiduciary duty to shareholders only.⁸ If the general

⁵ Hanson & Yosifon, *The Situational Character*, *supra* note 2, at 7–8 (citations omitted).

⁶ See Caplan, *supra* note 1.

⁷ KATHARINE GREIDER, *THE BIG FIX: HOW THE PHARMACEUTICAL INDUSTRY RIPS OFF AMERICAN CONSUMERS* 174 (2003).

⁸ See, e.g., Einer Elhauge, *Sacrificing Corporate Profits in the Public Interest*, 80 N.Y.U. L. REV. 733, 733 n.1 (2005). This is merely the mainstream view amongst judges and

consensus among legal academics is correct and this is indeed the law, it is illegal for a manager to make a decision that serves non-shareholder constituencies (e.g., employees, the environment, consumers, etc.) if such a decision fails to maximize shareholder wealth. A corporate manager that does so could theoretically be subject to criminal prosecution.⁹ Thus, a CEO of a pharmaceutical company would arguably be risking jail time if she chose to provide the indigent with free drugs.¹⁰

C. Implications for this Article

This Article purports to address the issues that plague consumers of pharmaceuticals with an understanding that, no matter what balanced research and writing reveals, the drug industry is not inherently evil. Unlike the psychologists who predicted that only 0.1% of subjects would shock all the way to “Danger! XXX!,” this Article will proceed with an eye toward the situational influences that shape industry behavior. The regulatory framework that society has given to

legal academics. *Id.* As Professor Elhauge’s article demonstrates, there is a rather large minority of commentators who disagree that this is in fact the law, and suggest that sound policy counsels against such rigid fiduciary duties. *See generally id.*

⁹ This analysis assumes that the majority of legal commentators are correct in their assumption that corporate managers owe a fiduciary duty to shareholders *only*. *See supra* note 8. In practice, courts almost never find that a breach of fiduciary duty has occurred simply because a company makes a decision that appears to be for the benefit of non-shareholder constituencies. *Dodge v. Ford Motor Co.* is certainly the exception rather than the rule. 204 Mich. 459 (Mich. 1919). In that case, Henry Ford, the CEO of Ford Motor Company, announced to the public that his company was reinvesting its profits instead of issuing dividends, and had chosen to do so because he wanted “to employ still more men; to spread the benefits of this industrial system to the greatest possible number, to help them build up their lives and their homes.” *Id.* at 468. The court held that the company had violated its fiduciary duty to shareholders, since Mr. Ford’s public statement indicated that the company was reinvesting its profits not for the benefit of its owners, but for the benefit of its workers and the public at large. *Id.* at 507. *Ford Motor Co.* sent a clear message to corporate managers around the world: “If you have interests beyond shareholder wealth maximization, do not disclose them.” Some companies still make public statements which suggest that corporate decisions are being made with an eye toward the interests of non-shareholders. *See, e.g.,* Aetna, Transforming Health Care in America, <http://www.aetna.com/about/america/> (stating that “Aetna values ethical business principles and socially responsible actions in our business practices, policy leadership, charitable giving, and community involvement.”). It is nevertheless difficult to prove impropriety, since corporate managers can always argue that the public appearance of benevolence and altruism is likely to produce more wealth for shareholders. *See* Henry Hansmann & Reinier Kraakman, *The End of History for Corporate Law*, 89 GEO. L.J. 439, 440–41 (2001).

¹⁰ This example assumes that the CEO’s act of charity was not a profit-maximizing decision. Managers can always argue that donations are in shareholders’ financial interests since they serve to boost the goodwill of the company.

drug companies, in which firms have no choice but to operate, is broken. Corporate managers are supposed to serve shareholder interests alone since the rest of our law—tort law, the tax code, criminal statutes, etc.—is supposed to protect non-shareholder constituencies against exploitation.¹¹ If pharmaceutical companies' profit-minded behavior is failing to optimize the public health, then the problem lies not with the firms themselves, but with the "other law" that is supposed to protect non-shareholder constituencies. A legal regime that provides drug companies with an incentive to engage in suboptimal research is equally as unfair to industry as it is to consumers. Big Pharma¹² is not the culprit, but rather another victim, as it is being forced to choose between honoring its fiduciary obligations to shareholders and advancing the public health. The good news is that situational forces are easier to sculpt than deeply ingrained dispositions. Just as Milgram's subjects responded differently when the experiment site was moved away from Yale, so too will Big Pharma change its behavior in the face of situational alterations designed to align the interests of consumers and industry.

III. TINKERING WITH THE PROTOCOLS:
INCENTIVES TO USE RESEARCH METHODS THAT FAIL TO MAXIMALLY
INFORM THE MEDICAL COMMUNITY
BUT ARE MORE LIKELY TO YIELD POSITIVE RESULTS

A. *The Correlation between Industry Funding and Positive Results*

Commercial sponsors provide approximately seventy percent of the funding for clinical drug trials in the United States.¹³ Numerous studies document the tight correlation between industry funding and published trial results that tout the safety and effectiveness¹⁴ of the

¹¹ See Hansmann & Kraakman, *supra* note 9.

¹² "Big Pharma" is a "term used to describe the global collective of research-based pharmaceutical companies, of which there are an estimated 75-100." JEFFREY ROBINSON, *PRESCRIPTION GAMES* 1 (2001).

¹³ Michelle M. Mello et al., *Academic Medical Centers' Standards for Clinical-Trial Agreements with Industry*, 352 *NEW ENG. J. MED.* 2202, 2202 (2005).

¹⁴ It is important to distinguish between "efficacy" and "effectiveness." The World Health Organization defines clinical effectiveness as "the likelihood and extent of desired clinically relevant effects in patients with the specified indication." Lisa A. Bero & Drummond Rennie, *Influences on the Quality of Published Drug Studies*, 12 *INT'L J. TECH. ASSESSMENT HEALTH CARE* 209, 209 (1996) (citing WHO, *18th European Symposium on Clinical Pharmacological Evaluation in Drug Control*, WHO Doc. 1993 EUR/ICP/DSE 173 (Dec. 10-13, 1991)). Efficacy, however, refers to "any arbitrarily chosen effect which may or may not be clinically relevant." *Id.*

drug in question.¹⁵ The literature offers three plausible explanations for the favorable results seen in industry-sponsored research.¹⁶ First, pharmaceutical companies may only fund research on the most promising compounds, refusing to finance trials in which failure is a substantial possibility.¹⁷ Second, industry representatives may be more reluctant than academics to publish the results of failed clinical trials.¹⁸ Finally, the methodology of industry-sponsored trials may be more likely to yield favorable results than the research methods¹⁹ of publicly funded studies.²⁰ This Article addresses the last of the three possibilities.

B. Increased Industry Control over the Design of Trials

Over the last two decades, pharmaceutical companies have acquired significantly more control over the design of the trials they sponsor.²¹ In the late 1990s, most drug companies did not have the

¹⁵ See Caplan, *supra* note 1.

¹⁶ Joel Lexchin et al., *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, 326 BRIT. MED. J. 1167, 1169–70 (2003) [hereinafter Lexchin et al., *Industry Sponsorship*].

¹⁷ Julio S. G. Montaner et al., *Industry-Sponsored Clinical Research: A Double-Edged Sword*, 358 LANCET 1893, 1893 (2001); Lexchin et al., *Industry Sponsorship*, *supra* note 16, at 1169.

¹⁸ Lexchin et al., *Industry Sponsorship*, *supra* note 16, 1170.

¹⁹ This paper uses the terms “methodology” and “research methods” interchangeably.

²⁰ Lexchin et al., *Industry Sponsorship*, *supra* note 16, at 1170. Lexchin et al. provide four explanations for the favorable results seen in industry-sponsored research. Whereas they identify two separate mechanisms through which industry can utilize research methods that are more likely to yield positive results, this paper combines them into one explanation. The first mechanism identified by Lexchin et al. is truly flawed research methodology, where the data produced is statistically invalid because the analysis of the data was mathematically unsound or the control group was treated differently from the experimental group in a manner other than the difference being tested by the trial. The second mechanism is a specific type of suboptimal, but unflawed trial, where the trial uses an inappropriate comparator. For example, if a company is attempting to prove that a new drug is more efficacious than an older alternative, the designer of the protocol may suggest a comparatively higher dose of the newer drug. See *infra* notes 31–36 and accompanying text for a discussion of the difference between trials that are methodologically flawed and those that are methodologically suboptimal. See *infra* Part III.E.v (discussing the use of inappropriate comparators).

²¹ MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES 29–30, 100–01, 103, 165–66, 244–47 (2004) [hereinafter ANGELL, THE TRUTH]; Thomas Bodenheimer, *Un-easy Alliance: Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539, 1541 (2000). Although the majority of this Article focuses on voluntary, post-approval studies not intended to support a label change, this section (entitled “Increased Industry Control over the Design of Trials”) speaks to all clinical trials (phases I–IV).

in-house experience to design protocols themselves.²² Nowadays, however, industry employs top-level research physicians to do the work.²³ Moreover, much of the research funded by industry has shifted from academic medical centers to Contract Research Organizations (CROs) and Site Management Organizations (SMOs), for-profit companies that specialize in the implementation of protocols and analysis of data.²⁴ Clinical investigators at CROs are generally thought to allow industry sponsors more leeway in designing protocols than investigators at academic medical centers.²⁵ Today, even academic medical centers do not have much input into the design of clinical trials; although company and academic investigators sometimes form a steering committee to discuss a trial protocol, industry traditionally writes the protocol, and brings in outside investigators pro forma, with little intention of changing the study design.²⁶

C. *Questioning the Findings that the Research Methods of Industry-Sponsored Studies are at Least as Good as Publicly Financed Trials*

Several studies have found that the research methods of industry-sponsored studies are at least as good, if not better, than the research methods of taxpayer-financed trials.²⁷ These studies, however, do not preclude the possibility that industry representatives tend to design trials differently from disinterested academics in a way

²² Some commentators contend that Bodenheimer may “overstate his point,” insofar as industry has been designing its own protocols since the 1950s. Author’s Personal Communication with Peter Hutt, Nov. 2005. The extent to which pharmaceutical companies have acquired more control over designing trials, however, is largely irrelevant to the point this section attempts to make. Whether industry is new to the game or not, no one disputes that firms today play an integral role in trial design.

²³ Bodenheimer, *supra* note 21, at 1540.

²⁴ COMMONWEALTH FUND, FROM BENCH TO BEDSIDE: PRESERVING THE RESEARCH MISSION OF ACADEMIC HEALTH CENTERS 31 (1999); Bodenheimer, *supra* note 21, at 1540; Lisa Henderson, *The Ups and Downs of SMO Usage*, CENTERWATCH MONTHLY NEWSLETTER, May 1999, at 4–8; Regina E. Herzlinger, *Schering-Plough and Genome Therapeutics: Discovering an Asthma Gene* (Harv. Bus. Sch. Case No. 9-303-044, Aug. 27, 2004).

²⁵ Bodenheimer, *supra* note 21, at 1540–41 (“In-house control is more likely in the commercial sector than in the academic sector, because of the limited expertise of many community-physician investigators.”).

²⁶ *Id.* at 1541. Once again, some commentators argue that Bodenheimer may “overstate his point.” See *supra* note 22. Regardless of whether the details of Bodenheimer’s writing are accurate, the fact that industry often exerts significant influence over trial design remains largely undisputed.

²⁷ See, e.g., Bodil Als-Nielsen et al., *Association of Funding and Conclusions in Randomized Drug Trials: A Reflection of Treatment Effect or Adverse Events*, 290 JAMA 921, 925–26 (2003); Lexchin et al., *Industry Sponsorship*, *supra* note 16, at 1170.

that renders favorable results more probable. This is true for three reasons.

First, the methodology used to determine the quality of the research methods does not preclude the possibility of bias.²⁸ The thirteen studies that found that the research methods of industry-sponsored trials were at least as good as those in publicly-financed trials utilized relatively crude mechanisms for evaluating quality.²⁹ The instruments used to test the methodological quality of clinical trials generally seek to determine only whether “systematic bias” has been minimized,³⁰ where systematic bias is defined as “anything that erroneously influences the conclusions about groups and distorts comparisons.”³¹ In other words, the quality-measuring instruments determine whether the statistical analyses were performed correctly and whether the experimental and control groups were identical in every respect, except for the particular difference being examined.³² They do not, however, provide insight into whether the trial’s time frame was optimal for detecting adverse side effects, the subjects were representative of the patient population likely to be treated with the medication, or inappropriate dosages were used to make the drug in question appear more effective.³³

In essence, the difference is one between trials that are methodologically flawed and those that are methodologically suboptimal. Flawed trials produce results that are scientifically invalid. Once it has been shown that investigators assigned subjects to comparison groups in a nonrandom manner, investigators and/or patients were unmasked, or the statistical analyses were corrupted, one can objectively say that the data are less reliable than that which would be produced by unflawed research methods. A methodologically subopti-

²⁸ Lexchin et al.’s meta-analysis admits this: “[T]he methodology used to determine the quality of research methods does not guarantee the absence of bias in studies sponsored by industry since outcome could be influenced by factors left out of quality scores, such as the question asked or the conduct or reporting of the study.” Lexchin et al., *Industry Sponsorship*, *supra* note 16, at 1170.

²⁹ *See id.* at 1168.

³⁰ Mildred K. Cho & Lisa A. Bero, *The Quality of Drug Studies Published in Symposium Proceedings*, 124 ANNALS INTERNAL MED. 485, 486 (1996).

³¹ Trisha Greenhalgh, *How to Read a Paper: Assessing the Methodological Quality of Published Papers*, 315 BRIT. MED. J. 305, 306 (1997).

³² *Id.*; see Tammy J. Clifford et al., *Funding Source, Trial Outcome and Reporting Quality: Are They Related? Results of a Pilot Study*, 2 BMC HEALTH SERVICES RESEARCH 18 (2002) (describing the Jadad scale, the most commonly used instrument for measuring methodological quality), <http://www.biomedcentral.com/1472-6963/2/18>.

³³ *See infra* Part III.E (discussing the myriad ways in which pharmaceutical sponsors may design trials in ways that are not ideal for testing the effectiveness or safety of the drug but are more likely to yield favorable results).

mal trial, however, produces valid data; the trial is merely less informative to the prescribing public than the optimal trial design. Unlike the case with flaws, the presence or absence of a methodologically suboptimal design is dependent on the cost associated with improving the trial, and is thus always open to debate. A sponsor who fails to enroll subjects who are representative of the group likely to take a drug may have done so in order to obscure the pharmaceutical's effect in the unrepresented group, or because the additional cost associated with enrolling those subjects would not have been cost-justified.³⁴ A methodological limitation can be said to exist in the former situation, but not the latter.³⁵

The thirteen studies that applaud the sound research methods of industry-sponsored trials generally examined flaws, rather than "limitations."³⁶ In any of the thirteen studies, an industry-funded trial could receive a perfect quality score even if different research methods would have been more informative to prescribing physicians.

Second, the studies analyzing the methodological quality of clinical trials fail to look at the difference between trials where the protocol was designed by pharmaceutical companies, and trials where disinterested academics had full control over trial design; they instead focus on the source of funding. One cannot assume that the protocols of all industry-funded trials are designed by industry while disinterested parties always design publicly-financed studies.³⁷ The

³⁴ There are many valid reasons for excluding particular subjects from a clinical trial. Enrichment trials, for example, enroll only those patients who are likely to benefit from a drug. Including subjects who are known not to benefit from the compound would not only be economically unsound, but unethical as well. My point is simply that *some reasons* for excluding particular types of subjects are improper, namely if the exclusion occurs in order to obscure the pharmaceutical's effect on the omitted group. The temptation to engage in such a practice exists only when a drug has already been approved by the FDA for the population excluded from the study, indicating that the compound does benefit these patients to some extent and therefore an enrichment trial would be inappropriate. *See infra* Part III.E.iii, viii. In essence, any time a drug works better in group A than in group B, but still met the required efficacy and safety thresholds to receive FDA approval in group B, the sponsor has an incentive to design a post-marketing study that enrolls a disproportionate number of people from group A.

³⁵ As this paragraph suggests, all flawed trials are suboptimal by definition, but suboptimal trials are not always flawed.

³⁶ I use the word "limitations" to signify a trial with suboptimal but unflawed research methods. Some of the thirteen studies do include methodological limitations in their analysis, but for the most part, the focus here is on methodological flaws.

³⁷ *See* Caitlin R. Reed & Carlos A. Camargo, *Recent Trends and Controversies in Industry-sponsored Clinical Trials*, 6 ACAD. EMERGENCY MED. 833, 855 (1999) (discussing the difference between industry-sponsored research and industry-initiated research, where company scientists "develop the idea, design the study, and write the proto-

correlation between industry sponsorship and unencumbered industry design may be imperfect enough to obscure a correlation between industry design and bias.

Finally, the thirteen studies concluding that industry-sponsored research methods are at least as sound as those designed by non-industry representatives fail to isolate post-approval (phase IV) clinical trials for analysis. Pharmaceutical companies have little incentive to design suboptimal protocols for phase I, II, and III trials since the FDA is privy to the research methods and results of all such trials when evaluating products for approval.³⁸ The submission of research data from methodologically suboptimal trials would reduce a company's chances of obtaining approval for all desired conditions and subpopulations.³⁹ It may make sense, however, for a drug company to

col"). The pervasiveness of academic researchers with financial ties to pharmaceutical companies makes it likely that someone who has a monetary stake in the outcome will design a publicly funded trial. See Marcia Angell, *Is Academic Medicine for Sale?*, 342 *NEW ENG. J. MED.* 1516, 1516–18 (2000) (offering an excellent discussion of the ubiquity of financial conflicts of interest); see generally JEROME P. KASSIRER, *ON THE TAKE* (2005). Furthermore, even if the trial designer remains financially non-conflicted, she may have an incentive to achieve favorable results since doing so will make the study more publishable and hence more valuable to her curriculum vitae.

³⁸ U.S. Food & Drug Admin., FDA New Drug Application (NDA) Process <http://www.fda.gov/CDER/regulatory/applications/nda.htm> (last visited Oct. 7, 2007); Oxigene Clinical Trial Patient Inquiries, <http://www.oxigene.com/prodDel.asp?sf=t> (last visited Oct. 7, 2007).

³⁹ In theory, there may be two circumstances where it would be in a firm's best interest to design suboptimal phase I, II or III trials that are more likely to yield favorable results. First, if the company could craft a protocol that interjects bias so subtle that the FDA cannot recognize it, the firm would profit from doing so. Second, if the company were certain that it will get approval for all desired conditions and subpopulations because of clear and convincing data, it could conduct methodologically suboptimal trials on other conditions and/or sub-populations for which it had no chance of obtaining approval. If clear and convincing data virtually ensured FDA approval for all desired conditions and subpopulations, the firm might even try to generate studies that inflate the effectiveness and/or safety of the drug, so that these studies can be used in its marketing efforts (e.g., by sales representatives). For instance, if the sponsoring firm knew that the only way it could obtain significant market share was to beat out a competitor, it might have an incentive to conduct perfect placebo-controlled studies but suboptimal head-to-head studies with the competition. AstraZeneca appears to have done this with Nexium since it knew that a substantial share of the market was unattainable unless it demonstrated that Nexium offered advantages over generic Prilosec—the company designed trials that used higher doses of Nexium than Prilosec, thereby making it look as if Nexium was more effective at treating heartburn. See *infra* Part III.E.v.c (discussing pharmaceutical companies' potential incentives to manipulate the dosing in industry-sponsored studies in order to achieve favorable results); see also ANGELL, *THE TRUTH*, *supra* note 21, at 76–79 (discussing in greater detail the events that led up to the poorly designed Nexium trials). The results of these suboptimal studies would have no effect on the FDA's decision since the company will conduct enough methodologically sound studies to obtain approval for all desired conditions and subpopulations, but can be used to influence

design a suboptimal phase IV protocol if (a) the post-marketing study is not required by the FDA,⁴⁰ and (b) the sponsoring firm has no intentions of seeking a label change from the FDA.⁴¹ The results of such a study can be published in journals and used by sales representatives to influence physicians' prescribing habits. So long as the methodology of the study is not flawed, but merely suboptimal, companies should have no trouble publishing the results.⁴² After all, a suboptimal but unflawed study still presents statistically sound data.⁴³

D. Building on the Work of Bero and Rennie: What this Article Adds to the Literature

Bero and Rennie published an article in 1996 that discussed the primary areas where bias might enter into the design, conduct or publication of a clinical trial.⁴⁴ Despite the fact that their paper has been consistently lauded,⁴⁵ little has been done to update or expand upon the research. This Article purports to build on Bero and Rennie's work in seven ways. First, it documents recent examples of industry-funded, methodologically suboptimal, published trials. Second, it broadens some of the categories of methodological limitations so that problems in future trials can be more easily recognized. Third, by subdividing the categories of suboptimal designs, this Article fleshes out several mechanisms through which methodological limitations may be introduced into a trial. Fourth, it identifies methodological limitations not discussed by Bero and Rennie. Fifth, this Article presents suggestions for further research that could empiri-

prescribing habits (e.g., convince doctors to prescribe the drug for off-label uses). In essence, such a trial would be a phase IV trial with a "head start" since its purpose would be the same as a phase IV study but the data would be available immediately after FDA approval.

⁴⁰ The FDA exerts significant influence over the design of *required* post-marketing studies. U.S. Food & Drug Admin., Post-Marketing Commitments, <http://www.fda.gov/cder/pmc/default.htm>.

⁴¹ The FDA's decision whether or not to grant a request to change the drug's label would undoubtedly consider the soundness of the post-marketing studies' methodology.

⁴² See *infra* Part III.E (providing a plethora of examples where prestigious medical journals published methodologically suboptimal, and in some cases flawed, trials).

⁴³ Lexchin et al. demonstrate that this is the case when they state that the research methods of industry-sponsored studies are at least as high quality as those of publicly-funded trials, since the level of "systematic bias" is no greater in the former than in the latter. Lexchin et al., *Industry Sponsorship*, *supra* note 16, at 1170; see *supra* notes 31–32 and accompanying text (offering a definition of "systematic bias").

⁴⁴ Bero & Rennie, *supra* note 14, at 228–29.

⁴⁵ JOHN ABRAMSON, *OVERDOSED AMERICA* 227 (2004); Bodenheimer, *supra* note 21, at 1541.

cally determine whether the pharmaceutical industry is in fact intentionally designing suboptimal protocols that are more likely to yield favorable results. Sixth, it demonstrates why, under the current legal/regulatory regime, the FDA, providers, payers, journal editors and the tort system are unable to eliminate methodological limitations in clinical trials. Finally, after examining proposals from other authors, this Article offers a novel solution for curbing industry's incentive to create suboptimal protocols.⁴⁶

E. Targeted Clinical Trials: Examples of Suboptimal Research Methods

(i) Introduction

The focus of this Article is on theory, not practice. This section discusses the many ways in which pharmaceutical companies *may have an incentive* to conduct methodologically suboptimal trials, providing examples of such studies merely as illustrations, rather than proof of intentional bias within industry-funded endeavors. Since no study has been conducted that proves or disproves the theory that drug companies intentionally design suboptimal protocols that are more likely to produce positive results, any discussion of actual instances where the results of methodologically suboptimal trials were published can be nothing more than anecdotal. Nevertheless, as this Article's discussion of the fundamental attribution error demonstrates, what matters most is not whether one can prove that commercially designed trials are statistically more likely to contain methodological limitations than protocols created without industry influence, but whether pharmaceutical companies are sometimes given an incentive to utilize suboptimal research methods.⁴⁷ A system that forces industry sponsors to choose between their legal obligation to maximize shareholder wealth and serving the public health through the design of maximally informative clinical trials is misguided, regardless of whether pharmaceutical companies are consistently choosing to honor their fiduciary duty to shareholders. In this very important sense, the theoretical is much more potent than the actual. Under-

⁴⁶ This Article also differs from the work of Bero and Rennie insofar as it focuses on methodological limitations, omitting any discussion of methodological flaws or issues surrounding the publication of trial results. I focus on methodological limitations, rather than flaws, for two principal reasons. First, some limit was needed in order to keep the scope of this Article manageable. Second, and more importantly, limitations are more difficult to prevent than flaws since the latter can be unambiguously identified by physicians, insurers and journal editors, while the existence of the former is dependent on the sponsor's cost structure and therefore open to debate.

⁴⁷ See *supra* Part II (discussing the fundamental attribution error).

standing the potential conflicts of interest in the design of clinical trials—what this Article purports to articulate—is far more important than determining how pharmaceutical companies tend to resolve those conflicts.

Many of the examples of suboptimal designs are presented hypothetically. This is done primarily because of the difficulty associated with combing the medical literature and identifying improperly targeted research. As discussed in Part III.C, the presence or absence of a methodological limitation is dependent on the cost associated with improving the trial, and is thus always open to debate. A protocol is suboptimal if and only if the benefits associated with the absent data outweigh the cost of making the results more informative to the prescribing public. Since it is difficult (if not impossible) for journal editors to determine whether a targeted trial is indicative of suboptimally informative research methods or a cost-justified limitation that serves the public health,⁴⁸ it would have been impossible to do so in this Article.⁴⁹ In any event, as there is no evidence that industry acts on the perverse incentives described in this Article, real world examples may not exist for all categories of methodological limitations.

Several of the hypothetical examples of suboptimal trial designs are created from real world examples of egregious errors in reporting. Such fraudulent reporting tends to highlight the perverse incentives that *future* trial designers are likely to face. For instance, the CLASS study discussed in Parts III.E.ii.a and III.E.iv.c failed to include data collected during the second six months of the trial. If the data were sufficiently damning to spur outright fraud, one would think that future designers of voluntary, non-label-seeking, post-approval studies would attempt to avoid the collection of such data altogether by conducting an unduly short trial.⁵⁰

Finally, it is important to reiterate that this Article addresses only voluntary post-approval trials not intended to support supplemental New Drug Application (NDA) labeling changes. The perverse incentives discussed below likely do not exist for other types of studies.

⁴⁸ See *infra* Part IV.A.v (discussing why journal editors are unable to curb industry's incentive to design targeted trials that do not serve the public health).

⁴⁹ See *infra* Part III.E.vii (discussing other reasons, besides cost, why it may be difficult to identify the existence of suboptimal methodology).

⁵⁰ See *infra* Part III.E.ii.a.

(ii) Time Frame: Conducting a Trial that Does Not Last Long Enough

Pharmaceutical companies may have an incentive to conduct studies that are unduly short. By terminating a trial earlier than is best for the medical community, industry sponsors may be able to limit the occurrence of adverse side effects and/or enhance perceived effectiveness.

(a) Limiting the Occurrence of Adverse Side Effects

Adverse side effects associated with pharmaceuticals often arise only after the patient has been taking the medication for an extended period of time.⁵¹ This is frequently true even in cases where the compound's desired therapeutic effects appear immediately after administration of the first dose.⁵² Pharmaceutical companies may therefore have an incentive to design a protocol that lasts long enough to demonstrate the desired efficacy but not long enough to reveal the adverse effects associated with the compound.⁵³ In some cases, a study may be done that is designed to measure adverse effects only, leaving efficacy to be determined by other trials.⁵⁴ In such a case, an industry sponsor may have an incentive to run a study that ends just before one would expect to begin seeing adverse side effects.

The September 13, 2000 issue of the Journal of the American Medical Association (JAMA) published the results of the CLASS study, a phase IV trial that compared the risk of gastrointestinal problems in people taking Celebrex with the risk in those taking ibuprofen and diclofenac.⁵⁵ The published results of the CLASS study have

⁵¹ U.S. Food & Drug Admin., Center for Drug Evaluation and Research, *Clinical Therapeutics and the Recognition of Drug-Induced Disease, A MedWatch Continuing Education Article*, June 1995, at 1, available at <http://www.fda.gov/medwatch/articles/dig/ceart.pdf> (last visited Oct. 7, 2007).

⁵² *Id.* at 2.

⁵³ Generally speaking, only after a drug has become a blockbuster can a company afford to run a long-term trial with enough subjects to identify a rare side effect with statistical significance. Such cost considerations are clearly valid concerns that should affect the scope of clinical studies. A problem arises not when a sponsoring firm forgoes a fishing expedition for a rare side effect, but rather when it knowingly shortens a trial because of evidence suggesting that side effects are likely to become increasingly prevalent as time passes.

⁵⁴ See Bero & Rennie, *supra* note 14, at 212–13 (discussing the tendency to define research questions too narrowly so that efficacy and safety are not proven in the same study).

⁵⁵ Fred E. Silverstein et al., *Gastrointestinal Toxicity with Celecoxib vs. Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis: The CLASS Study: A Randomized Controlled Trial*, 284 JAMA 1247 (2000).

been extensively criticized for failing to disclose pertinent information about the trial.⁵⁶ Although the study was run for a full twelve months, the authors submitted data from only the first six months for the article in JAMA.⁵⁷ The authors failed to report that, during the second six months of the study, “six of the seven serious gastrointestinal complications that occurred were in patients taking Celebrex.”⁵⁸

For purposes of this paper, the important point is not that Pharmacia, the maker of Celebrex, concealed data, but rather that future industry representatives designing trials for Cox-2 Inhibitors or similar compounds may be wary of recording data on gastrointestinal complications for more than six months.⁵⁹ If, prior to conducting the CLASS study, Pharmacia had any indication that gastrointestinal problems were far more likely to occur after six months of use, the company would have had an incentive to limit the phase IV study to a six-month time frame.⁶⁰ Alternatively, if Pharmacia had not concealed the data, it could have run a subsequent six-month study in an effort to control some of the damage.⁶¹

⁵⁶ ABRAMSON, *supra* note 45, at 29–33 (providing an excellent, easy to understand account of the issues surrounding JAMA’s presentation of the CLASS study); ANGELL, THE TRUTH, *supra* note 21, at 108–109; Greider, *supra* note 7, at 102.

⁵⁷ ABRAMSON, *supra* note 45, at 29; Susan Okie, *Missing Data on Celebrex Full Study Altered Picture of Drug*, WASH. POST, Aug. 5, 2001, at A11.

⁵⁸ ABRAMSON, *supra* note 45, at 29; Okie, *supra* note 57.

⁵⁹ Celebrex is a Cox-2 inhibitor.

⁶⁰ One could argue that required phase IV studies provide an adequate check against the interjection of such bias, insofar as the FDA would never have approved Celebrex without a promise by Pharmacia to measure gastrointestinal side effects for at least twelve months. Such an argument, however, ignores the reality that pharmaceutical companies routinely fail to conduct FDA-mandated post-approval trials. *See FDA Requested Postmarketing Studies in 73% of Recent New Drug Approvals*, TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT IMPACT REPORT, Jul.–Aug. 2004, at 1–4 (K.I. Kaitin, ed.) (stating that the completion rate for required post-marketing studies from 1998–2003 was twenty-four percent).

⁶¹ In this particular case, it might not be profitable for Pharmacia to conduct a second study since doing so would be costly and the financial return associated with the damage control would be dubious. The prevalence of gastrointestinal problems was so much higher during the second six months of the CLASS study than the first six months that many doctors would likely recognize the bias inherent in the second, purposefully shortened trial. In another case, however, where there is not such a large discrepancy in the adverse effects between the early and late stages of the initial trial, it might make financial sense for a company to conduct a second, methodologically suboptimal study. Without the precipitous increase in complications seen in the CLASS study, more doctors might fail to recognize the methodological limitation of the second trial.

(b) Enhancing Perceived Effectiveness

In addition to limiting the occurrence of adverse effects, shortening the length of a study may enhance perceived effectiveness. A drug may be excellent at treating the symptoms of a chronic disease for a short period of time, but not nearly as efficacious over the long run as the patient becomes habituated to the medication. Studies purporting to test the effectiveness of Selective Serotonin Reuptake Inhibitors (SSRIs) at treating depression have been criticized for being too short.⁶² Since SSRIs become less effective over time⁶³ and, even in studies of just four to eight weeks, the drug typically fails to statistically outperform a placebo or outperforms it by a very small margin,⁶⁴ it would seem that pharmaceutical companies have an incentive to design voluntary, non-label-seeking, post-approval studies that are as short as possible.⁶⁵

(c) Identifying the Presence of a Problem

The solution to the problem of unduly short trials is not to mandate lengthier studies across the board, but rather to realign the incentives of trial designers with the public health. A blanket requirement to extend studies would increase the cost of each trial, thereby reducing the amount of money left in the sponsor's research and de-

⁶² See, e.g., JOSEPH GLENMULLEN, PROZAC BACKLASH: OVERCOMING THE DANGERS OF PROZAC, ZOLOFT, PAXIL AND OTHER ANTIDEPRESSANTS WITH SAFE, EFFECTIVE ALTERNATIVES 205 (2000).

⁶³ See Tony Kendrick, *Prescribing Antidepressants in General Practice*, 313 BRIT. MED. J. 829 (1996); see also Duncan B. Double, Letter, *Prescribing antidepressants in general practice*, 314 BRIT. MED. J. 826, 826 (1997).

⁶⁴ GLENMULLEN, *supra* note 62, at 207. This point should not be taken as evidence that SSRIs are worthless drugs that offer marginal benefits in *all* cases. To the contrary, it is likely that SSRIs are quite effective in some cases and wholly ineffective in others but current science is unable to adequately screen out those patients who do not respond favorably to the medication. Nevertheless, since there is no way to screen out the non-responders, clinical trial designers are left with a high hurdle (proof of effectiveness) and limited power with which to clear that hurdle (the responders must exhibit greater levels of effectiveness than would be necessary if non-responders could be systematically removed from the study). Thus, industry sponsors have an incentive to recruit hurdle-clearing power by shortening the length of the trials.

⁶⁵ This argument does not suggest that sponsors *always* have an incentive to design unduly short trials. Such an incentive only exists when there is some evidence to suggest that the compound's effectiveness will decline with time (or adverse side effects will become more prevalent). Indeed, if there is good evidence to suggest that the drug's long-term safety and effectiveness profile will mirror its short-term profile (as is the case with statins), industry sponsors have a financial incentive to conduct a longer study that proves this point.

velopment budget to examine other drugs.⁶⁶ Firms must be given incentives to design trials that are optimal in length, insofar as shorter studies would fail to produce enough data about the drug's safety and effectiveness, while the additional funding needed for longer studies could be put to better use in the administration of other trials.

(iii) Inappropriate Subjects: The Use of Patients Who Are Less Likely to Experience Adverse Side Effects and/or More Likely to Demonstrate Efficacy

Pharmaceutical companies may have an incentive to improperly enroll a study population that is unrepresentative of the patients taking the medication, but for which success (low adverse side effects and/or high efficacy) is likely.⁶⁷ Any time a drug works better in group A than group B, but still meets the required efficacy and safety thresholds to receive FDA approval in group B, the manufacturer may have an incentive to design trials that enroll a disproportionate number of subjects from group A. Of course, there are numerous *valid* reasons for excluding subpopulations from a trial. For instance, there may be evidence that the drug is ineffective for a certain group. In such a case, including the subpopulation for which the drug would have no effect would not only be economically unsound, but unethical as well. This section focuses exclusively on situations in which industry sponsors may have an improper incentive to exclude certain patients from a trial—i.e., where the patient population is narrowed in order to obscure the pharmaceutical's effect on the excluded group.⁶⁸ In essence, when past studies have demonstrated that a drug is safer and/or more effective in group A than in group B, but still sufficiently safe and effective in group B to have received FDA approval, the sponsor may have an incentive to conduct a "quasi-enrichment trial." An economically rational sponsor will attempt to enroll as many patients from group A as possible (getting as close to a full enrichment trial as possible) without going so far as to prompt complaints from competitors or alert perspicacious physicians to the enrichment-like nature of the trial. The percentage of patients from group A that a sponsor has an incentive to enroll will also turn on the extent to which the drug is superior for subpopulation A. If the drug

⁶⁶ In theory, pharmaceutical companies could continue conducting research at the same rate by expanding the research and development budget and raising prices, reducing other expenditures, or accepting lower profits.

⁶⁷ Bero & Rennie, *supra* note 14, at 213.

⁶⁸ See *infra* Part III.E.vii (discussing some of the valid reasons for excluding certain types of patients from clinical trials).

is remarkably safer and/or more effective in group A (as opposed to only marginally superior), physicians are more likely to notice if the study population has been improperly enriched with individuals from group A.

(a) Age

Industry sponsors may have an incentive to enroll patients who are younger than those taking the drug since favorable results are generally harder to obtain in elderly subjects.⁶⁹ Although individuals sixty-five years of age and older consume approximately one-third of all drugs,⁷⁰ they are severely underrepresented in clinical trials.⁷¹ Senior citizens are among the largest users of anti-inflammatory drugs and are more likely to suffer serious complications from their use.⁷² Nevertheless, only 2.1 percent of patients in studies of anti-inflammatory drugs are over the age of sixty-five.⁷³ Although three-fourths of the patients in a typical cancer trial are under age sixty-five, approximately two-thirds of all cancer patients are sixty-five or older.⁷⁴ Despite the fact that half of the men who have strokes are seventy-one or older while half of the women who have strokes are seventy-nine or older,⁷⁵ a recent study examining the risk of stroke in patients taking Pravachol⁷⁶ enrolled patients with an average age of sixty-two.⁷⁷ Although the study touted the effectiveness of Pravachol in lowering the risk of stroke, a closer analysis of the details reveals that the “patients in the study age 70 and older who had been treated with Prava-

⁶⁹ Jerry Avorn, *Including Elderly People in Clinical Trials: Better Information Could Improve the Effectiveness and Safety of Drug Use*, 315 BRIT. MED. J. 1033, 1033–34 (1997); Bero & Rennie, *supra* note 14, at 213. Of course, there are many valid reasons for excluding the elderly from clinical trials. See *infra* Part III.E.vii.

⁷⁰ Avorn, *supra* note 69, at 1033.

⁷¹ G. Bugeja et al., *Exclusion of Elderly People from Clinical Research: A Descriptive Study of Published Reports*, 315 BRIT. MED. J. 1059, 1059 (1997); Jerry H. Gurwitz et al., *The Exclusion of the Elderly and Women from Clinical Trials in Acute Myocardial Infarction*, 268 JAMA 1417, 1417 (1992).

⁷² Paula A. Rochon et al., *The Evolution of Clinical Trials: Inclusion and Representation*, 159 CANADIAN MED. ASS'N J. 1373, 1373 (1998); see ABRAMSON, *supra* note 45, at 103–04 (offering an excellent discussion of the under-representation of elderly patients in clinical trials).

⁷³ Rochon et al., *supra* note 72, at 1373.

⁷⁴ ABRAMSON, *supra* note 45, at 104.

⁷⁵ *Id.* at 16.

⁷⁶ Pravachol is the brand name of Pravastatin, a cholesterol-lowering statin drug.

⁷⁷ Harvey D. White et al., *Pravastatin Therapy and the Risk of Stroke*, 343 NEW ENG. J. MED. 317, 318 (2000).

chol actually had 21 percent *more* strokes than the patients given a placebo.”⁷⁸

(b) Race

In some circumstances, pharmaceutical companies may have an improper incentive to enroll a disproportionate number of subjects from a particular race. BiDil, a medication used to treat heart failure in African American patients, recently became the first drug to receive FDA approval for use in a specific racial group.⁷⁹ In 1999, the makers of BiDil attempted to obtain FDA approval for the use of the drug in all races, but the FDA concluded that the required efficacy had not been demonstrated.⁸⁰ The data in the 1999 NDA suggested that the medication was more effective in African Americans, and thus the FDA advised NitroMed, the current manufacturer of the drug, to conduct studies on African Americans alone so that they could obtain race-targeted approval for BiDil.⁸¹ If BiDil had been barely effective enough in Caucasians to receive approval from the FDA in 1999 for use in all races (but still far more effective for African Americans), NitroMed⁸² might have had an incentive to conduct voluntary, non-label-seeking phase IV studies in which the subjects are disproportionately African American.

(c) Gender

The Pravachol study discussed above provides an example of how industry sponsors may have a perverse incentive to enroll a disproportionate number of subjects from one gender.⁸³ Although sixty percent of stroke victims are women, eighty-three percent of the people enrolled in the Pravachol study were men.⁸⁴ Despite the authors' praising remarks for Pravachol's overall effectiveness, buried in the details of the study is the fact that the “women in the study who were

⁷⁸ ABRAMSON, *supra* note 45, at 16.

⁷⁹ U.S. Food & Drug Admin., *FDA Approves BiDil Heart Failure Drug for Black Patients*, June 23, 2005, <http://www.fda.gov/bbs/topics/NEWS/2005/NEW01190.html> (last visited Oct. 7, 2007).

⁸⁰ Aaron Lorenzo, *FDA Panel Votes 9-0 to Support BiDil's Clearance*, BIOWORLD TODAY, June 17, 2005, at 7.

⁸¹ *Id.*

⁸² “Medco Research” is the name of the company that submitted the NDA in 1999. If approval had been granted for all races in 1999, NitroMed might not have acquired the rights to the patent. The name “Nitromed,” however, is used for simplicity.

⁸³ See *supra* notes 76–79 and accompanying text (discussing the Pravachol study).

⁸⁴ ABRAMSON, *supra* note 45 at 16; White et al., *supra* note 77.

given Pravachol experienced 26 percent *more* strokes than the women who were given a placebo.”⁸⁵ Whenever a drug is safer and/or more effective for one gender, but still sufficiently safe and effective to have received FDA approval for both men and women, industry may have an incentive to conduct voluntary, non-label-seeking phase IV studies that selectively enroll one gender.

(d) Severity of the Disease

Designers of industry-sponsored studies may have an incentive to enroll subjects with mild forms of the disease in question, even though the drug is used regularly in patients with more serious symptoms. Some have criticized antidepressant studies for excluding individuals who are severely depressed or suicidal.⁸⁶

Many drugs receive FDA approval for only the mild to moderate form of the disease, and thus may not be marketed for more severe types of the illness.⁸⁷ In some cases, a drug may reach the efficacy and safety thresholds necessary to receive FDA approval for severe forms of the disease, even though the drug is better suited for mild to moderate symptoms.⁸⁸ In such a case, industry sponsors may have a financial incentive to design voluntary, non-label-seeking phase IV studies in which a disproportionate number of mild to moderate sufferers are enrolled. If the reverse is true, and a drug is approved for all forms of the disease but is safer and/or more effective in more severe sufferers, firms may have an incentive to exclude individuals with mild symptoms from phase IV trials.⁸⁹

⁸⁵ ABRAMSON, *supra* note 45 at 16.

⁸⁶ See GLENMULLEN, *supra* note 62, at 205; see also Nat'l Inst. of Mental Health, Antidepressant Medications for Children and Adolescents: Information for Parents and Caregivers, http://www.nimh.nih.gov/healthinformation/antidepressant_child.cfm (last visited Oct. 7, 2007).

⁸⁷ Consider Aricept, a medication approved to treat mild to moderate forms of Alzheimer's Disease. See *Aricept (Donepezil) Shows Significant Benefits In Moderate/Severe Alzheimer's Disease*, DOCTOR'S GUIDE—GLOBAL EDITION, Aug. 28, 2001, <http://www.pslgroup.com/dg/204B9E.htm> (last visited Oct. 7, 2007); see also GlaxoSmithKline, *Coreg (carvedilol) Receives FDA Approval for Treatment of Severe Heart Failure*, http://www.gsk.com/press_archive/press_11012001.htm (last visited Oct. 7, 2007) (discussing Coreg, a heart failure medication originally approved for only mild to moderate forms of the disease but later approved to treat severe conditions).

⁸⁸ *Id.*

⁸⁹ See GlaxoSmithKline, *Requip (Ropinirole HCl) Tablets First and Only Medication Approved by the FDA for the Treatment of Moderate-to-severe Primary Restless Leg Syndrome (RLS) in Adults*, <http://www.gsk.com/ControllerServlet?appId=4&pageId=402&newsId=485> (last visited Oct. 7, 2007).

(e) Miscellaneous

There are an infinite number of ways in which an industry sponsor may possess incentives to select subjects that are not representative of the patient class receiving (or likely to receive) the drug but more likely to yield favorable results. As discussed previously, any time a drug works better in group A than group B, but still meets the required efficacy and safety thresholds to receive FDA approval in group B, the manufacturer may have an incentive to design trials that enroll a disproportionate number of subjects from group A. Pharmaceutical companies may feel pressure to exclude from trials individuals who possess comorbidities or take other medications than the one being studied.⁹⁰ Alternatively, they may have an incentive to purposefully select subjects who are using drugs that make a favorable response from the compound in question more likely.

For example, consider the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, a post-approval trial that compared the risk of serious gastrointestinal problems in people treated with Vioxx against those treated with naproxen.⁹¹ Although only a small percentage of the people taking Vioxx at the time the study was conducted and published took steroids at the same time, over half of the people included in the VIGOR study were taking steroids for their arthritis.⁹² Notwithstanding the VIGOR study's conclusion that Vioxx "is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen,"⁹³ a close analysis of the article reveals that the "reduction in the risk of gastrointestinal complications was not large enough to be statistically significant" among the subjects not taking steroids.⁹⁴ In the Pravachol study discussed above,⁹⁵ "five out of six patients in the study were taking aspirin routinely," although the vast majority of the general public does not.⁹⁶ As in the VIGOR study, the Pravachol trial lauded the effectiveness of the drug in question, glossing over the fact that, among the people in the study who were not taking aspirin, those taking

⁹⁰ ABRAMSON, *supra* note 45, at 103–04; GLENMULLEN, *supra* note 62, at 205. Quite often, such exclusion will be entirely appropriate. See *infra* Part III.E.vii. I speak only to the situation where medical knowledge would be optimized by including such patients in trials.

⁹¹ Claire Bombardier et al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 NEW ENG. J. MED. 1520 (2000).

⁹² ABRAMSON, *supra* note 45, at 33.

⁹³ Bombardier et al., *supra* note 91, at 1520.

⁹⁴ ABRAMSON, *supra* note 45, at 33.

⁹⁵ White et al., *supra* note 77.

⁹⁶ ABRAMSON, *supra* note 45, at 16.

Pravachol had twenty percent more strokes than those taking placebos.⁹⁷

(f) Rebutting the Economic Argument

Even in cases where there is no argument that the drug in question is ineffective or harmful for the excluded group, pharmaceutical companies may be able to argue that the public health is served by removing certain patients from post-approval studies. Utilizing a heterogeneous population may destroy the value of a narrowly-focused study, requiring additional data collection or larger samples to achieve the same study power.⁹⁸ This may increase the cost of clinical trials and therefore raise the price of drugs or reduce innovation. Although such an argument has merit, it does not adequately address the issues discussed in this section. This is true for two reasons.

First, although an economic argument can be made for excluding the elderly, individuals with severe symptoms, or patients with comorbidities, there is *generally* no justification for selecting patients who take another drug not commonly used by the general public, or reason for disproportionately favoring one gender or race.⁹⁹ Second, although in some cases, the money saved by narrowing the focus of the research (e.g., by excluding elderly subjects) outweighs the augmentation of medical knowledge associated with having data from a variety of patients, this is not always true. Often, the public health would be better served by spending the money needed to enroll a heterogeneous study population, since doing so will help prevent serious adverse events in subpopulations that otherwise would have been underrepresented in the medical literature.¹⁰⁰ Under the current legal regime, firms may have an incentive to exclude patients from trials when their enrollment would enhance physicians' understanding of the drug to an extent that makes the increased cost of the trial economically justifiable. If pharmaceutical companies are going to continue to decide which subjects are to be enrolled in the studies

⁹⁷ *Id.*

⁹⁸ Avorn, *supra* note 69, at 1033.

⁹⁹ It may make economic sense to study only one race or only one gender insofar as doing so helps to narrow the research question, reducing the cost per unit of statistical power.

¹⁰⁰ Richard Smith, *What Clinical Information Do Doctors Need?*, 313 BRIT. MED. J. 1062 (1996). Enrolling a heterogeneous study population may be economically efficient even if adverse side effects are not prevented by the more diverse enrollment. If a physician's understanding of the drug's effectiveness, safety, and/or cost-effectiveness in the otherwise under-represented patient population is increased to an extent that outweighs the increased cost of the trial, then it makes economic sense to broaden the study population.

they sponsor, society has a duty to ensure that the interests of industry representatives are adequately aligned with the public health.

(iv) Inappropriate Measures of Efficacy and Safety

Pharmaceutical companies may have an incentive to design trials so that a drug's efficacy and/or safety is measured in ways that fail to maximally advance physicians' knowledge of the medication, but are more likely to yield favorable results.¹⁰¹

(a) Measuring Surrogate End Points Rather Than Clinical Outcomes

When determining a drug's effectiveness, trials will ideally use primary endpoints, clinically relevant events of which a patient is aware and wants to avoid.¹⁰² For example, a study of a medication used to treat heart disease might test whether users of the drug experience a lower incidence of cardiac death than those taking placebos. Intermediate or surrogate endpoints are outcomes that, in and of themselves, are meaningless to the patient since their only value lies in their correlation with primary endpoints.¹⁰³ Examples of surrogate endpoints are the level of cholesterol in the blood or one's blood pressure, since patients are interested in such measures only because of their correlation with overall cardiac health. It is rational and reasonable for study designers to use surrogate endpoints when primary outcomes are too difficult and/or expensive to measure routinely, and when the surrogate endpoint is sufficiently well-correlated with the primary outcome.¹⁰⁴

Industry-sponsored studies, however, may have an incentive to use surrogate outcomes even when primary endpoints are easily measurable and/or the surrogate outcome is only loosely correlated with the endpoint of true clinical significance.¹⁰⁵ If a drug is more effective at inducing or preventing a surrogate outcome than the primary endpoint for which it received FDA approval, pharmaceutical

¹⁰¹ Bero & Rennie, *supra* note 14, at 219. Bero and Rennie discuss how bias may be introduced by measuring too many outcomes, so that some outcomes appear statistically significant just by chance. As such bias would result in statistically invalid data, it is an example of a methodological flaw, rather than a limitation. A discussion of this topic is therefore beyond the scope of this Article.

¹⁰² Eva Lonn, *The Use of Surrogate Endpoints in Clinical Trials: Focus on Clinical Trials in Cardiovascular Diseases*, 10 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 497, 498 (2001).

¹⁰³ *Id.*

¹⁰⁴ Susan S. Ellenberg & J. M. Hamilton, *Surrogate Endpoints in Clinical Trials: Ophthalmologic Disorders*, 8 STAT. MED. 427, 430 (1989).

¹⁰⁵ Bero & Rennie, *supra* note 14, at 219.

companies may have an incentive to conduct voluntary, non-label-seeking, post-marketing studies that utilize the surrogate endpoint as the outcome of interest.¹⁰⁶ This may be true regardless of how easy or inexpensive it is to test a more clinically relevant outcome, or how poorly correlated the surrogate endpoint is with the primary endpoint.

An example of such perverse incentives may be found with many new osteoporosis drugs.¹⁰⁷ Although post-menopausal women primarily lose trabecular bone (the internal, lattice-like bone), osteoporosis medications are most effective at generating cortical bone (the hard, dense, outer layer).¹⁰⁸ The additional cortical bone increases patients' scores on bone density tests but does not necessarily reduce the incidence of fractures.¹⁰⁹ Clinical trials designed to evaluate the effectiveness of osteoporosis drugs often use bone density tests as a surrogate endpoint, even though there may be a very poor correlation between one's score on a bone density test and the prevention of fractures.¹¹⁰

¹⁰⁶ FDA approval may be granted on the basis of research using surrogate endpoints alone, but the reviewers must feel confident that the surrogate outcome was used justifiably insofar as the relationship between the two endpoints has been sufficiently proven and/or the primary endpoint is too difficult and/or costly to measure directly. See Robert Temple, *Are Surrogate Markers Adequate to Assess Cardiovascular Disease Drugs?*, 282 JAMA 790, 791–92 (1999) (discussing the issues surrounding FDA approval of drugs tested solely or primarily with surrogate endpoints).

¹⁰⁷ See ABRAMSON, *supra* note 45, at 210–20.

¹⁰⁸ *Id.* at 216.

¹⁰⁹ *Id.* at 216–217.

¹¹⁰ See Carolyn J. Green et al., *Informing, Advising or Persuading? An Assessment of Bone Mineral Density Testing Information from Consumer Health Web Sites*, 20 INT'L J. TECH. ASSESSMENT HEALTH CARE 1 (2004); Michael R. McClung et al., *Effect of Risedronate on the Risk of Hip Fracture in Elderly Women*, 344 NEW ENG. J. MED. 333, 333 (2001) (stating in article abstract that “[r]isedronate increases bone mineral density in elderly women, but whether it prevents hip fracture is not known.”). The FDA takes the position that new osteoporosis drugs must demonstrate a reduction in fractures, as increased bone density is not sufficiently correlated with such a reduction. See U.S. Food & Drug Admin., *Guidelines for Preclinical and Clinical Evaluation Agents Used In the Prevention or Treatment of Postmenopausal Osteoporosis*, Apr. 1994, available at <http://www.fda.gov/cder/guidance/osteop.pdf>. The guidelines state that:

The most important morbid event in osteoporosis is fracture. . . . In epidemiologic studies, bone mineral density (BMD) has predicted the risk of vertebral fracture. However, a treatment related increase in BMD cannot be assumed to result in reduced risk of fracture. For example, the relationship between BMD and fracture risk has been validated only for patients receiving estrogens, and does not apply to patients receiving fluoride.

Id.

Of course, if physicians were always aware of the tenuous correlation between bone mineral density and protection against fractures, little harm could come from

(b) Custom-tailoring Measures of Effectiveness to the Drug
in Question

Syndromes are clusters of symptoms that typically occur together and are thus presumed to be related.¹¹¹ In contrast with a disease like diabetes or cancer, the only way to tell if a patient suffers from a particular syndrome is to compare her symptoms with those typically reported by an afflicted individual; medical tests (e.g., x-rays, CAT scans) are not capable of confirming the presence or absence of a syndrome.¹¹² When designing voluntary, non-label-seeking, phase IV studies to determine a drug's effectiveness in the treatment of a syndrome, pharmaceutical companies may have an incentive to focus on the symptoms that the company believes are most likely to respond to the medication. For instance, suppose a syndrome is characterized by symptoms A through F, and the industry sponsor knows for certain that the drug in question significantly ameliorates symptoms A through C, but is less confident of the medication's effect on symptoms D through F because the compound's effect on these symptoms was barely sufficient to obtain FDA approval in the first place. In such a case, the firm may feel pressure to design a trial that puts more emphasis on symptoms A through C when measuring the extent to which subjects suffer from the syndrome.¹¹³ The degree to which trial designers have an incentive to unduly focus on symptoms A through C will likely turn on the extent to which the drug is superior for these symptoms. If the drug is remarkably less effective for symptoms D through F (as opposed to only marginally inferior), physicians are more likely to notice that the measurement scale does not give equal weight to all symptoms.

the use of the surrogate endpoint. Some articles, however, are not as candid as the study conducted by McClung et al., insofar as the uncertain relationship between bone mineral density and fractures may not be expressly mentioned. Moreover, when detailing physicians on post-approval trials pharmaceutical sales representatives typically do not provide physicians with copies of the entire study and may not discuss the correlation between the surrogate and primary endpoints.

¹¹¹ See WEBSTER'S NINTH NEW COLLEGIATE DICTIONARY 1197 (9th ed. 1986).

¹¹² Inst. for the Study of Healthcare Orgs. and Trans., *Psychiatric Diagnosis*, <http://www.institute-shot.com/Psychiatric%20Diagnosis.htm> (last visited Oct. 7, 2007) (including an extended draft of an article to appear in *Alternatives to the DSM*, a text published by the American Psychological Association, and edited by L. E. Beutler and M. L. Malik).

¹¹³ See Daniel J. Safer, *Design and Reporting Modifications in Industry-Sponsored Comparative Psychopharmacology Trials*, 190 J. NERV. MENT. DIS. 583, 584 (2002) (discussing "self-serving measurement scales" in psychopharmacological trials).

An example of this may be found in studies on depression, which, like all psychiatric diagnoses, is a syndrome.¹¹⁴ The degree to which one suffers from depression is often measured quantitatively using checklist rating scales such as the Zung Self-Rating Scale for patients and the Hamilton Depression Scale for technician-raters who interview patients.¹¹⁵ The scales ask patients to indicate whether they “get tired for no reason,” “have trouble sleeping at night,” “feel downhearted and blue,” etc.¹¹⁶ When designing non-required post-marketing trials, pharmaceutical companies may feel pressure to employ scales that emphasize the physical symptoms of depression most susceptible to pharmacological intervention.¹¹⁷

(c) Inappropriately Broadening or Narrowing of Categories

A pharmaceutical company sponsoring a voluntary, non-label-seeking post-approval clinical trial may have an incentive to design the study so that the drug’s adverse side effects are categorized in a way that is suboptimal in terms of advancing the medical literature, but more likely to produce favorable results. If the sponsor is aware that the drug causes side effect X, it may be reluctant to design a trial in which the occurrence of X in the study population is independently measured. Instead, the company may feel pressure to use a protocol that requires clinical investigators to group together side effects X, Y, and Z, where X, Y and Z are related in some fashion (e.g., they are all cardiac side effects). The investigators may have an incentive to refrain from recording data on the occurrence of individual side effects, only recording the frequency of X, Y and Z as a group.

Alternatively, another drug may present a scenario in which the public health would be best served by aggregating several types of complications, but separate analyses allow the company to report more favorable results. Such a situation, however, is far less problematic because the data obtained from measuring the side effects separately may be combined to produce the desired information. When aggregation produces favorable results but individual analysis does not, it may be impossible to produce the preferred information, since

¹¹⁴ AM. PSYCHIATRIC ASSOC., DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, at xxx–xxxii (Michael B. First, M.D. et al. eds., 4th ed. 2000).

¹¹⁵ GLENMULLEN, *supra* note 62, at 206.

¹¹⁶ *Id.*

¹¹⁷ GLENMULLEN, *supra* note 62, at 206; DAVID HEALY, THE ANTIDEPRESSANT ERA 76 (1997).

data pertaining to the individual adverse effects may not have been recorded.

As discussed above, the CLASS study was an FDA-mandated, phase IV trial that compared the risk of gastrointestinal problems in people taking Celebrex with the risk in those taking ibuprofen and diclofenac.¹¹⁸ The original research design, submitted to the FDA by Pharmacia, was lauded by the agency's gastroenterology reviewer for recording and analyzing the occurrence of clinically significant (major)¹¹⁹ gastrointestinal side effects separately from the incidence of less serious gastrointestinal problems.¹²⁰ When the study was published in JAMA, however, the incidences of clinically significant and minor gastrointestinal side effects were combined.¹²¹ The categories of adverse side effects were broadened because the original study design failed to show that Celebrex users developed significantly less gastrointestinal complications than users of ibuprofen or diclofenac.¹²² Statistically significant evidence to support the proposition that Celebrex is safer than other NSAIDs could be obtained only by aggregating the data from major and minor side effects.

As was the case with Pharmacia's decision to conceal the data from the last six months of the trial, the important point is not that the company distorted data and deceived the editors of JAMA.¹²³ The point is that industry sponsors of future voluntary, non-label-seeking post-marketing trials testing the safety of Cox-2 inhibitors or similar compounds may have an incentive to design studies that fail to differentiate between the occurrence of major and minor gastrointestinal complications, even though doing so would be in the best interests of the public health. If, prior to conducting the CLASS study, Pharmacia had any indication that combining the data would be vital, it would have had a perverse incentive to obtain FDA-approval of a

¹¹⁸ Silverstein et al., *supra* note 55, at 1247–50.

¹¹⁹ The term “clinically significant” generally refers to side effects that require hospitalization. See ABRAMSON, *supra* note 45, at 31.

¹²⁰ U.S. Food & Drug Admin., FDA Arthritis Advisory Committee, *Briefing Information: Celebrex (celecoxib)*, Feb. 7, 2000, at 8, available at http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_05_gi.pdf. “The establishment of a CSUGIE [clinically significant upper gastrointestinal event] . . . as the primary endpoint with the addition of symptomatic ulcers only as a secondary endpoint is a major strength of the current study . . .” *Id.*; see ABRAMSON, *supra* note 45, at 31.

¹²¹ Silverstein et al., *supra* note 55, at 1250–54.

¹²² ABRAMSON, *supra* note 45, at 31. This is true even when the last six months of data were excluded from the analysis. See *supra* notes 55–61 and accompanying text (discussing how Pharmacia concealed the data from the last half of the trial).

¹²³ *Id.*

phase IV study that did not separately record major and minor events.¹²⁴ In this case, data pertaining to the individual classes of side effects existed and thus it was possible to conclude that Celebrix's claim of superior safety rested on the methodological limitation. In the future, if an industry sponsor has the forethought to design a trial in which such data is not collected, it will be impossible for reviewers of the study to determine whether different research methods would have had an effect on the statistical significance of the results.

(v) Inappropriate Comparators

When conducting voluntary, non-label-seeking post-approval studies, pharmaceutical companies may have an incentive to use a control that is cheap and provides the best chance of obtaining favorable results, even though a different comparator would be more medically informative.¹²⁵ Ray et al. describe an example of how NIH-sponsored studies used appropriate comparison groups, whereas industry-funded trials of the same drugs did not.¹²⁶ Lexchin et al. suggest that the selection of inappropriate comparators may be a major reason why industry-sponsored studies are more likely to yield favorable results.¹²⁷

(a) Placebo Control Versus Head-to-Head Trials

A pharmaceutical company designing a voluntary, non-label-seeking phase IV trial may have an incentive to compare their drug to a placebo even though it would be more beneficial to doctors if the study utilized standard, preexisting therapies as comparators. In some cases, head-to-head trials may provide physicians with information, which cannot be obtained from placebo-controlled studies, about whether the new drug is more effective and/or safer than alternative treatments.

¹²⁴ In the case of the CLASS study, it is likely that the FDA would not have approved a study that did not record data separately for major and minor events. However, industry sponsors of future, *non-required*, non-label-seeking, post-approval studies may have an incentive to design such a protocol.

¹²⁵ Bero & Rennie, *supra* note 14, at 216. This methodological limitation likely affects trials in earlier phases as well, since the FDA considers placebo-controlled studies to be adequate for obtaining approval. See 21 C.F.R. § 314.126 (2007). Indeed, the FDA generally demands placebo-controlled studies unless it would be unethical to deprive the control population of therapy.

¹²⁶ See Wayne A. Ray et al., *Evaluating Drugs After their Approval for Clinical Use*, 329 NEW ENG. J. MED. 2029, 2030 (1993).

¹²⁷ Lexchin et al., *Industry Sponsorship*, *supra* note 16, at 1170.

Djulgovic et al. evaluated the appropriateness of the comparators in clinical trials and determined that industry-sponsored studies are more likely than publicly-funded trials to compare innovative treatment to either placebo or no therapy.¹²⁸ Studies sponsored by public resources were more likely to compare the drug in question with alternative treatments.¹²⁹

Critics of the pharmaceutical industry contend that the majority of compounds developed by companies are “me-too” or “follow-on” drugs,¹³⁰ drugs that the FDA does not consider to be significant improvements over other therapies. According to the critics, the firms avoid head-to-head trials (opting instead for placebo-controlled studies) because there is a much higher risk of obtaining damaging results when an alternative treatment is used as a comparator.¹³¹ In other words, the companies are relatively confident that their me-too drugs are more effective than placebos, and it’s not in their financial interest to conduct a study to determine if their drug is better than existing treatments.

Some critics have gone so far as to suggest that the Food and Drug Administration should condition approval on the results of head-to-head trials proving the new drug’s superiority over other therapies.¹³² This seems rather extreme and counterproductive, since placebo-controlled studies are significantly cheaper than those using pharmacologic interventions as comparators,¹³³ and in some cases, the marginal advancement in medical knowledge created by the head-to-head trial may not justify the decline in research that follows

¹²⁸ Benjamin Djulgovic et al., *The Uncertainty Principle and Industry-sponsored Research*, 356 LANCET 635, 637 (2000).

¹²⁹ It is true that the FDA generally requires placebo-controlled studies for phases I-III, but such a fact does not explain why industry sponsors are less likely to utilize therapeutic comparators.

¹³⁰ See, e.g., ANGELL, THE TRUTH, *supra* note 21, at 74–93; Marcia Angell, *The Pharmaceutical Industry—To Whom is it Accountable?*, 342 NEW ENG. J. MED. 1902, 1903 (2000).

¹³¹ *Id.* at 75–76.

¹³² ANGELL, THE TRUTH, *supra* note 21, at 240; Bero & Rennie, *supra* note 14, at 229.

¹³³ Placebo-controlled studies are cheaper than head-to-head studies not only because the comparison therapy costs more in the latter, but because head-to-head trials require many more subjects. See John R. Graham, *Using our Heads on Head-to-Head Trials*, FRASER FORUM, Feb. 2003, at 6, available at http://www.fraserinstitute.org/Commerce.Web/product_files/Using%20our%20Heads%20on%20Head-to-Head%20Trials-Graham.pdf (last visited Oct. 10, 2007). As is indicated by the FDA’s preference for placebo-controlled trials, it is often the case that using a placebo comparator is not only cheaper than using a therapeutic comparator, but scientifically superior as well.

from the increased cost of conducting clinical trials. The proper approach is to align the incentives of the pharmaceutical industry with the public health so that non-placebo comparators are used when (and only when) the subsequent advancement of the medical literature outweighs the increased cost of the study.

(b) Poorly Represented Interventions: Generics, Dietary Supplements and Lifestyle Modifications

Pharmaceutical companies may have an incentive to conduct placebo-controlled studies when the public health would be best served by comparing the drug in question with inexpensive, alternative therapies such as generic drugs (alternative compounds that have gone off patent), dietary supplements, or lifestyle modifications.¹³⁴ Although such study design is a specific example of the problem discussed above (companies' failure to conduct head-to-head trials), it deserves a category of its own since its effect on the medical literature and the issuance of prescriptions is especially pernicious. In circumstances where the public health calls for brand name competition as a comparator but the industry sponsor designs a placebo-controlled study, physicians and insurers will still have information (albeit imperfect information) about both therapies. The manufacturers of the brand-name competition that should have been used as the comparator will conduct their own placebo-controlled trials.¹³⁵ Prescribers and health plans attempting to determine which drugs it should place on formulary may be able to make a rough determination of the relative effectiveness and safety of the two drugs by analyzing the data from the placebo-controlled trials.¹³⁶

When industry sponsors fail to include generics, dietary supplements, or lifestyle modifications as comparators, prescribers and health plans generally have access to less information with which they can make comparisons between the drug and the omitted comparator. Although placebo-controlled trials always exist for generics, since

¹³⁴ Bero & Rennie, *supra* note 14, at 217; Ray et al., *supra* note 126, at 2029.

¹³⁵ Pharmaceutical companies must demonstrate that a drug is better than an appropriate control (usually placebo) before they can market the drug. See 21 C.F.R. § 314.126 (2007). The fact that the drug that should have been used as a comparator is still on patent indicates that these studies are relatively recent and generally quite accessible. See *infra* notes 137–142 and accompanying text (discussing why the studies of generic drugs may be less accessible).

¹³⁶ See *infra* Part IV.A.iv (discussing the role of health plans in preventing the use of suboptimal research methods).

such data is required by the FDA for approval,¹³⁷ the information may be accessed less for two reasons. First, the data pertaining to alternative, off-patent drugs is likely older and thus less likely to be available online.¹³⁸ Second, generic drug companies spend far less on marketing than the manufacturers of brand-name pharmaceuticals, and thus physicians are less likely to think of generic alternatives.¹³⁹ Unlike manufacturers of brand name drugs, companies producing generics generally do not employ pharmaceutical representatives who can alert physicians to the presence of data.¹⁴⁰ Data on the effectiveness of dietary supplements and lifestyle modifications may not exist since their efficacy does not have to be proven prior to marketing.¹⁴¹ Even if data is available, the lack of marketing for such interventions may make physicians less likely to suggest non-pharmaceutical alternatives.¹⁴²

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)¹⁴³ exemplifies the adverse impact of pharmaceutical companies' reluctance to use generic comparators, that is, to use alternative, off-patent drugs as comparators.¹⁴⁴ Although private drug companies helped fund the ALLHAT study, the vast majority of the money came from the National Heart, Lung, and Blood Institute, a branch of the National Institute of Health (NIH).¹⁴⁵ The trial compared four types of anti-hypertensive drugs: a calcium channel blocker, an alpha-adrenergic blocker, an angiotensin-

¹³⁷ 21 C.F.R. § 314.126. The placebo-controlled trials referred to are those that the FDA required for the drug to be approved in the first place (when it was still on patent).

¹³⁸ See, e.g., JAMA website, <http://jama.ama-assn.org/> (full text papers are generally only available for articles published after 1998).

¹³⁹ See Joel Lexchin, *Interactions Between Doctors and Pharmaceutical Sales Representatives*, 8 CANADIAN J. CLIN. PHARMACOL. 64 (2001) [hereinafter Lexchin, *Interactions*].

¹⁴⁰ *Id.*

¹⁴¹ See generally Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417 (1994).

¹⁴² Lexchin, *Interactions*, *supra* note 139.

¹⁴³ The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, *Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs. Diuretic*, 288 JAMA 2981 (2002) [hereinafter ALLHAT Research Group].

¹⁴⁴ ANGELL, *THE TRUTH*, *supra* note 21, at 95-99; JERRY AVORN, *POWERFUL MEDICINES* 273 (2004); Laurence K. Altman, *Older Way to Treat Hypertension Found Best*, N. Y. TIMES, Dec. 18, 2002, at A1.

¹⁴⁵ See Vasilios Papademetriou et al., *Characteristics and Lipid Distribution of a Large, High-Risk, Hypertensive Population: The Lipid-Lowering Component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)*, 5 J. CLINICAL HYPERTENSION 377 (2003); Ron Winslow & Scott Hensley, *Study Questions High-Cost Drugs for Hypertension*, WALL ST. J., Dec. 18, 2002, at A1.

converting enzyme (ACE) inhibitor, and a generic diuretic that had been on the market for over fifty years.¹⁴⁶ The study concluded that “[t]hiazide-type diuretics are superior in preventing 1 or more major forms of CVD [cardiovascular disease] and are less expensive . . . [and thus] should be preferred for first-step antihypertensive therapy.”¹⁴⁷ Prior to the study, diuretics cost about six times less than the next cheapest anti-hypertensive medication,¹⁴⁸ but were used much less frequently than calcium channel blockers,¹⁴⁹ alpha-adrenergic blockers or ACE inhibitors.¹⁵⁰ Given the large number of Americans who suffer from hypertension,¹⁵¹ and general concern over the rising cost of prescription drugs,¹⁵² the public had an interest in obtaining the results of the ALLHAT study years earlier, when diuretics began to be replaced by more expensive, brand name medications.¹⁵³ The fact that brand-name anti-hypertensive drugs were not compared with generic diuretics until years after they should have been, as well as the nature of ALLHAT’s funding, suggest that the pharmaceutical industry both possesses and acts on a perverse incentive to conduct placebo-controlled trials when the use of generic comparators would be more informative.

The April 11, 2005 edition of the Archives of Internal Medicine published a publicly-funded meta-analysis which concluded that omega-3 fatty acids (present in fish oil) are more effective than three lipid-lowering drugs (statins, fibrates, and resins) at preventing both

¹⁴⁶ ALLHAT Research Group, *supra* note 143, at 2981; ANGELL, THE TRUTH, *supra* note 21, at 96.

¹⁴⁷ ALLHAT Research Group, *supra* note 143, at 2981.

¹⁴⁸ Winslow & Hensley, *supra* note 145.

¹⁴⁹ *Id.* In 2002, Pfizer’s calcium channel blocker Norvasc was the fifth-best-selling drug in the world. See Press Release, IMS Health, IMS Reports 8 Percent Constant Dollar Growth in 2002 Audited Global Pharmaceutical Sales to \$400.6 Billion (Feb. 25, 2003), available at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_41336931,00.html.

¹⁵⁰ Winslow & Hensley, *supra* note 145. A list of the top fifty drugs used by senior citizens in 2001 contains Norvasc (Pfizer’s calcium channel blocker) and three brand-name ACE inhibitors, but does not contain any thiazide-type diuretics. See *Bitter Pill: The Rising Prices of Prescription Drugs for Older Americans*, FAMILIES USA, June 2002, at 11, available at <http://familiesusa.org/assets/pdfs/BitterPillreport74f9.pdf> (last visited October 7, 2007).

¹⁵¹ At least sixty-five million Americans suffer from hypertension. See, e.g., Rob Stein, *Number of Americans who have High Blood Pressure Up Sharply*, WASH. POST, Aug. 24, 2004, at A2.

¹⁵² See, e.g., Avorn, *supra* note 144, at 189–266.

¹⁵³ In 1982, diuretics accounted for fifty-six percent of prescriptions written for high blood pressure. See ANGELL, THE TRUTH, *supra* note 21, at 97. In 1992, however, after calcium channel blockers and ACE inhibitors hit the market, they accounted for only twenty-seven percent. *Id.*

cardiac death and death from any cause.¹⁵⁴ Given these results, it would seem that pharmaceutical companies sponsoring future voluntary, non-label-seeking post-approval studies of lipid-lowering drugs may have an incentive to design placebo-controlled trials even though the public would be best served by comparative data on omega-3 fatty acids. The article in the Archives of Internal Medicine concludes by suggesting that “[f]uture trials . . . explore whether n-3 [omega-3] fatty acids in combination with statins lead to additional reduction in CHD [coronary heart disease] mortality, especially in patients with metabolic syndrome.”¹⁵⁵ It is questionable whether industry sponsors will heed this advice, since manufacturers of statins have much to lose but little to gain from such studies unless they test healthy patients. Currently, anywhere between twelve and fifteen million Americans with elevated blood cholesterol take statins, and some experts are suggesting that it might be beneficial for individuals with normal serum cholesterol to take the drug.¹⁵⁶ Neither the American Heart Association nor the American College of Cardiology, however, recommend treating low-risk patients with statins since there is not enough data to support it.¹⁵⁷

In essence, statins dominate the market for the treatment of elevated serum cholesterol, but have room to expand by earning support for their use as preventive medicine in healthy individuals.¹⁵⁸ Just as the makers of calcium channel blockers, alpha-adrenergic blockers and ACE inhibitors had little incentive to compare their drug to a diuretic when diuretics captured such a small percentage of the market, statin manufacturers have little incentive to alert the public to the benefits of omega-3 fatty acids in patients with hypercholesterolemia. If studies conclude that statins and fish oil together reduce the risk of death more than fish oil alone in patients with elevated serum cholesterol, it will have a negligible impact on statin sales, since statins are already prescribed pervasively for hypercholesterolemia.¹⁵⁹ If studies conclude that statins and fish oil together are

¹⁵⁴ Marco Studer et al., *Effect of Different Antilipidemic Agents and Diets on Mortality: A Systemic Review*, 165 ARCHIVES INTERNAL MED. 725, 726–27 (2005).

¹⁵⁵ *Id.* at 729.

¹⁵⁶ Imaginis: The Women’s Health Source, *Study: Discontinuing Cholesterol-Lowering Drugs Harmful for Hospitalized Heart Disease Patients*, <http://www.imaginis.com/heart-disease/news/news6.22.02.asp> (last visited Oct. 10, 2007).

¹⁵⁷ *Id.*

¹⁵⁸ Bleys W. Rose, *The War on Cholesterol*, HERALD TRIBUNE.COM, Aug. 25, 2005, <http://www.newscoast.com/apps/pbcs.dll/article?AID=/FP/20050809/HEALTHMATTERS/50808001>.

¹⁵⁹ *Id.* Even if the addition of statins helps reduce the risk of death, it may make sense for physicians to prescribe fish oil alone since statins are associated with several

no more effective than fish oil alone at preventing death in patients with high cholesterol, statin manufacturers may lose market share as doctors begin to prescribe cheaper omega-3 supplementation instead of statins.

The incentive to compare the benefits of statins and fish oil together with each product alone in healthy patients may be minimal as well. Although statin manufacturers stand to increase sales if studies conclude that statins and fish oil together are more effective at preventing cardiac death and/or all-case mortality in patients without hypercholesterolemia, opposite results have the potential to foreclose the market for healthy consumers. Evidence has been mounting for some time that statins are a beneficial form of preventive medicine for low-risk patients.¹⁶⁰ Considering the progress being made toward expanding the market for statins into the realm of preventive medicine for healthy consumers, industry sponsors of clinical trials may find that the potential benefit of positive findings is small and thus do not outweigh the risk of adverse results. Companies may have an incentive to conduct placebo-controlled studies for patients with and without hypercholesterolemia even though society would be best served by understanding how lipid-lowering drugs stack up against cheaper dietary supplements.

As is the case with generic drugs and dietary supplements, pharmaceutical sponsors appear reluctant to design trials in which lifestyle modifications are used as comparators.¹⁶¹ Once again, the risk of finding out that lifestyle modifications are more effective than the drug in question is often too great to justify the use of head-to-head trials. Several studies have demonstrated that exercise training and smoking cessation greatly reduce the risk of adverse cardiovascular events in patients with weakened hearts.¹⁶² Nevertheless, when Guidant, the manufacturer of implantable defibrillators, conducted a phase IV trial to determine whether the prophylactic implantation of

side effects while the only side effect of omega-3 fatty acids is an unpleasant after-taste. See Omega-3 Fatty Acids, Wholehealthmd.com, http://www.wholehealthmd.com/refshelf/substances_view/1,1525,992,00.html (last visited Aug. 25, 2005); Schieszer, *supra* note 156; *Statins' Side Effects Under Fire*, CBSNEWS.COM, Oct. 12, 2004, <http://www.cbsnews.com/stories/2004/10/11/eveningnews/main648685.shtml> (last visited Oct. 7, 2007).

¹⁶⁰ Schieszer, *supra* note 156.

¹⁶¹ ABRAMSON, *supra* note 45, at 101.

¹⁶² See, e.g., Romualdo Belardinelli et al., *Randomized, Controlled Trial of Long-term Moderate Exercise Training in Chronic Heart Failure: Effects on Functional Capacity, Quality of Life, and Clinical Outcome*, 99 CIRCULATION 1173, 1173 (1999); Kumanan Wilson et al., *Effect of Smoking Cessation on Mortality after Myocardial Infarction: Meta-analysis of Cohort Studies*, 160 ARCHIVES INTERNAL MED. 939, 943 (2000).

a defibrillator in patients who have suffered a heart attack reduces the risk of death, no effort was made to determine whether defibrillators are more or less effective than counseling about the importance of exercise or smoking cessation.¹⁶³ Just as fish oil and statins together may be more effective than either alone, lifestyle counseling along with a cardiac defibrillator may be the best therapy for heart attack victims. Unfortunately, however, pharmaceutical companies have not been given the incentives needed to investigate the matter, and physicians are left in the dark.¹⁶⁴

(c) Inappropriate Dosing

Industry sponsors may feel pressure to manipulate the dosages of the test compound and non-placebo comparator in order to achieve more favorable results.¹⁶⁵ When designing a voluntary, non-label-seeking post-marketing trial to test the efficacy of a drug, pharmaceutical companies may have an incentive to use inappropriately high doses for the firm's product and/or inappropriately low doses for the comparator.¹⁶⁶ A 1994 study conducted by Rochon et al. concluded that forty-eight percent of industry-funded trials testing the effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) utilized a higher dose for the manufacturer's drug than the comparator.¹⁶⁷ Alternatively, when a study is meant to compare the adverse side effects associated with the sponsor's product with those of a competitor, industry sponsors may have an incentive to use low doses for the test compound and/or high doses for the comparator. Safer reported that commercially funded trials testing the relative side effects of different psychiatric drugs tend to employ inordinately high

¹⁶³ See Arthur J. Moss et al., *Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction*, 346 NEW ENG. J. MED. 877 (2002). *Contra* ABRAMSON, *supra* note 45, at 98–101 (discussing the shortcomings of the Moss study).

¹⁶⁴ Contrary to what may be popular belief, there is significant evidence that lifestyle counseling by physicians can be effective. See, e.g., Diabetes Prevention Research Group, *Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin*, 346 NEW ENG. J. MED. 393, 398 (2002); Jaakko Tuomilehto et al., *Prevention of Type 2 Diabetes Mellitus by Changes in Lifestyle among Subjects with Impaired Glucose Tolerance*, 344 NEW ENG. J. MED. 1343, 1348 (2001).

¹⁶⁵ Bero & Rennie, *supra* note 14, at 218.

¹⁶⁶ "Inappropriately high dosages" signifies dosages that are higher than those typically prescribed to patients while "inappropriately low dosages" signify dosages that are lower than those typically prescribed to patients.

¹⁶⁷ Paula A. Rochon et al., *A Study of Manufacturer-supported Trials of Nonsteroidal Anti-Inflammatory Drugs in the Treatment of Arthritis*, 154 ARCHIVES INTERNAL MED. 157, 159 (1994).

dosages of competitors' products.¹⁶⁸ If certain routes of administration for a drug are more effective or safer than others, pharmaceutical companies may have an incentive to compare their drug to the less attractive version of the competitor's product. For example, according to Johansen and Gotzsche, trials sponsored by manufacturers of fluconazole tended to compare their drug with oral, not intravenous, amphotericin B since the oral version is poorly absorbed.¹⁶⁹

(vi) Perfect Reporting Helps but does not Solve the Problem

Many of the perverse incentives discussed in Part III.E incorporate an element of inappropriate reporting as well as suboptimal trial design. The harm to society caused by methodological limitations would be significantly mitigated if published studies made it clear that the trial enrolled a disproportionate number of patients from certain subpopulations, focused on only some of the symptoms that comprise a syndrome, or refrained from collecting data on particular adverse events. Such disclosure, however, would not eliminate the problem. Society has an interest in obtaining certain information about the pharmaceuticals being marketed for sale. Suboptimal protocols deprive consumers and prescribers of this knowledge, regardless of whether the studies openly acknowledge that they do so. Adequate disclosure may reduce the risk that physicians will erroneously extrapolate data, but it does not optimally advance the scientific literature.

(vii) Ensuring that Limitations are Truly Limitation

As discussed throughout this Article, it is often perfectly acceptable (and indeed desirable) for industry trial designers to create shortened protocols, exclude subclasses of patients, utilize surrogate endpoints, refrain from conducting head-to-head trials and omit data on safety, effectiveness, or cost-effectiveness. This subsection briefly articulates some of the valid reasons, *besides cost* (which is discussed in Part III.C) for conducting trials that may *superficially* appear to contain methodological limitations.

Shortened trials and studies that fail to test a compound's safety or effectiveness are often socially optimal. Suppose evidence from phase I–III studies is sufficient to demonstrate a drug's long-term

¹⁶⁸ Safer, *supra* note 112, at 583–584.

¹⁶⁹ Helle Krogh Johansen & Peter C. Gotzsche, *Problems in the Design and Reporting of Trials of Antifungal Agents Encountered During Meta-analysis*, 282 JAMA 1752, 1752–53 (1999).

safety and the manufacturer merely wants to begin examining whether the compound would provide an immediate cure for another ailment. In such as case, it would be proper for the firm to conduct a shortened trial that only examines effectiveness.

Selectively enrolling patients from particular subpopulations is only problematic when it is done to obscure the pharmaceutical's effect on the excluded group. As discussed in Part III.E.iii, it would be unethical for a company *not* to exclude subpopulations for which there is evidence that the drug will be ineffective. Furthermore, enrichment trials are often preferred to studies that enroll all types of subjects because they provide better evidence of effectiveness.¹⁷⁰ In many instances, it is reasonable for trial designers to exclude the elderly since they disproportionately suffer from comorbid conditions and are thus more likely to confound results.¹⁷¹ And of course, there are often valid reasons for excluding children and women of child-bearing age.¹⁷²

As stated in Part III.E.iv.a, it is desirable for the industry to use surrogate endpoints when primary outcomes are too difficult and/or expensive to measure routinely, and when the surrogate endpoint is sufficiently well-correlated with the primary outcome. Indeed, the FDA approves many compounds based solely on studies that make use of surrogate outcomes.¹⁷³

Very often the public would not be best served by head-to-head trials. Not only are such studies incredibly costly, but placebo-controlled research is generally preferable for determining efficacy.¹⁷⁴ Indeed, placebo-controlled trials are a requirement for FDA approval unless such research would be unethical. Furthermore, in many cases, it would be pointless to determine which of several drugs in a particular class is "the best." Physicians often report that different compounds in the same class work for different patients, and trial

¹⁷⁰ Patrick Clinton & Jill Wechsler, *Whatever Happened to Critical Path*, PHARMACEUTICAL EXECUTIVE ONLINE, Jan. 2006, <http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=282481&searchString=Whatever%20Happened%20to%20Critical%20Path> (last visited Oct. 7, 2007).

¹⁷¹ Avorn, *supra* note 69, at 1033.

¹⁷² Harriette G. C. Van Spall et al., *Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals: A Systematic Sampling Review*, 297 JAMA 1233, 1237–40 (2007).

¹⁷³ See, e.g., Temple, *supra* note 106, at 793.

¹⁷⁴ Martin R Tramèr et al., *When Placebo Controlled Trials are Essential and Equivalence Trials are Inadequate*, 317 BRIT. MED. J. 875, 875–880 (1998) (stating in summary that "[i]n clinical settings where no gold standard treatment exists and where event rates vary widely, trial designs without placebo controls are unlikely to yield sensible results.").

and error is currently the only method available to determine who will respond to what medication.¹⁷⁵ Regardless of the results of head-to-head studies, physicians would still have to engage in the same trial and error process.

It is very difficult to identify which protocols are suboptimally designed and which are justifiably limited. Any proposed solution to the problem of methodological limitations must be tactically designed insofar as it ferrets out suboptimal research, leaving firms with an incentive to shorten trials, exclude patients and utilize surrogate outcomes when doing so is in the best interest of the public health.

(viii) Concluding Remarks

Under the current regulatory regime, pharmaceutical companies may have a financial incentive to design voluntary, non-label-seeking post-marketing studies that are suboptimal in terms of informing the medical community.¹⁷⁶ This is problematic for two reasons. First, society would be better served if industry's funding were allocated to more medically informative studies. Second, suboptimal protocols have the potential to deceive prescribers.¹⁷⁷ Although some physicians will recognize that alternative research methods would have been more helpful in determining the effectiveness, safety and/or cost-effectiveness of the drug, many will not.¹⁷⁸ These physicians, and even some who recognize the studies' shortcomings, may prescribe the drug when there is a safer, more effective, or less costly treatment.¹⁷⁹ Even if the FDA always required the studies necessary to give physicians the full picture (ensuring that they are methodologically perfect), and firms always complied without delay,¹⁸⁰ pharmaceutical companies might still have an opportunity and incentive to

¹⁷⁵ Joseph A. DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development: Trends in Entry Rates and the Timing of Development*, 22 PHARMACOECONOMICS 1, 11–12 (2004).

¹⁷⁶ If the company hopes to use the results of the phase IV study to gain FDA approval for another subpopulation or medical condition, then there is likely no incentive to design a suboptimal protocol. In such a case, the phase IV study would take on characteristics of a phase I, II, or III study since it would be conducted, at least in part, to obtain FDA approval. However, pharmaceutical companies may sometimes have an incentive to design methodologically improper phase I, II, or III trials. See *supra* note 40 and accompanying text.

¹⁷⁷ This is true even if there are no reporting errors in the studies. Physicians may not take the time to read the studies carefully, relying on pharmaceutical representatives to explain the details. See Lexchin, *Interactions*, *supra* note 139, at 64.

¹⁷⁸ *Id.*

¹⁷⁹ *Id.*

¹⁸⁰ As discussed, companies frequently fail to conduct FDA-mandated phase IV studies. See *supra* note 61.

run other voluntary, non-label-seeking, methodologically suboptimal post-approval studies. Many, if not most, physicians would not recall the details of the FDA-required studies, and certainly very few would take the time to compare the research methods of the methodologically perfect and suboptimal trials.¹⁸¹

There is no such thing as a perfectly designed clinical trial. To some extent, all trials will be suboptimally informative to the prescribing public. Nevertheless, we must strive to create a society in which trial designers, whether they are employed by industry, nonprofit organizations or taxpayers, have incentives (financial or otherwise) that are as closely aligned with the public health as possible.

F. Suggestions for Future Research

The focus of Part III.E was on theory, not practice. It is presently unclear whether pharmaceutical companies actually act on the perverse incentives described above. Future research should attempt to determine whether industry sponsors are indeed more likely than disinterested academics to design methodologically suboptimal protocols. It is important to compare data from industry-designed (as opposed to industry-funded) trials with those protocols created by entirely disinterested parties.¹⁸² One cannot assume that the protocols of all commercially-financed trials are designed by industry while disinterested parties always design publicly-funded studies.¹⁸³

Future research should keep in mind that the extent of pharmaceutical companies' influence over the design of protocols proceeds along a continuum.¹⁸⁴ When determining whether industry-designed trials are more likely to contain methodological limitations, one cannot simply check a box for "commercially designed" or "created by a disinterested team of academics." In some cases, the pharmaceutical company will have some influence over the trial design without possessing unfettered discretion.¹⁸⁵

Ideally, each trial examined should be given a score that represents the extent to which the study was designed by neutral parties or the sponsoring company, and investigators should determine

¹⁸¹ Lexchin, *Interactions*, *supra* note 139, at 64.

¹⁸² See *supra* note 38. It may be impossible to find someone who is "entirely disinterested" since academics have an incentive to advance their careers and positive findings may help to do so more than negative results. *Id.*

¹⁸³ *Id.*

¹⁸⁴ See generally Kevin. A. Schulman et. al., *A National Survey of Provisions in Clinical-Trial Agreements between Medical Schools and Industry Sponsors*, 347 NEW ENG. J. MED. 1335 (2002).

¹⁸⁵ *Id.*

whether there is a correlation between this score and the extent of methodological bias. Such rating, however, may be impossible in practice since pharmaceutical companies, academic medical centers, and contract research organizations (CROs) may be reluctant to divulge information surrounding the process through which the final protocol was created.¹⁸⁶ All parties may be hesitant to support the idea that they contributed to the production of suboptimal research by allowing an industry sponsor to retain significant control over a trial's design.

An alternative, albeit less perfect, mechanism for determining whether pharmaceutical companies purposefully design suboptimal trials may be to compare studies conducted by CROs with publicly-financed trials run by disinterested academics. Although administration by a CRO is an imperfect proxy for identifying protocols designed with extensive industry influence, it is more perfect than including all industry-funded trials, since academic medical centers conducting commercially-sponsored research may exhibit considerable influence over the design of a protocol.¹⁸⁷

As discussed throughout this Article, pharmaceutical companies have little incentive to design suboptimal protocols for phase I, II, and III trials since the FDA is privy to the research methods and results of all such trials when evaluating products for approval.¹⁸⁸ The submission of research data from methodologically suboptimal trials would reduce a company's chances of obtaining approval for all desired conditions and subpopulations. Therefore, future studies examining industry sponsors' ability to control clinical trial data by designing suboptimal protocols should separately analyze non-required post-approval studies (focusing, if possible, on trials in which the sponsor has no intention of seeking a label change from the FDA). Given that there are some circumstances in which it may be in a company's best interest to design suboptimal phase I, II, III, or re-

¹⁸⁶ The International Committee of Medical Journal Editors' (ICMJE) uniform requirements for manuscripts submitted to biomedical journals states that "authors should describe the role of the study sponsor(s), if any, in study design." See International Committee of Medical Journal Editors—Uniform Requirements for Manuscripts submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, updated Oct. 2004, <http://www.icmje.org/>. It is questionable, however, whether the authors' statements surrounding the role of the sponsor in the design of the protocol will be sufficient to rate trials according to the extent of commercial influence over the research methods. See Schulman et al., *supra* note 184 (discussing academic institutions' tendency to engage in industry-sponsored research that fails to adhere to ICMJE guidelines).

¹⁸⁷ See Bodenheimer, *supra* note 21, at 1543.

¹⁸⁸ See *supra* note 39.

quired phase IV studies,¹⁸⁹ future research may want to examine trials in all four phases. Investigators, however, should ensure that the sample of non-required (and ideally non-label-seeking) post-marketing trials is sufficiently large to generate statistically meaningful results.

This Article focuses solely on methodological limitations, ignoring entirely the issue of methodological flaws.¹⁹⁰ Several researchers have raised the possibility that industry-designed studies are more likely to contain flaws in the research methods that not only render the study suboptimally informative, but question the validity of the data as well.¹⁹¹ Although Lexchin et al. suggest that the research methods of industry-sponsored trials contain no more flaws than the research methods of publicly-financed trials,¹⁹² no study has been done that takes into account the fact that industry-funded trials may be designed without significant commercial influence and the idea that academic researchers may not be entirely disinterested. Moreover, no study has been conducted that separately analyzes voluntary, non-label-seeking, post-approval trials. Future studies should therefore investigate the prevalence of both flaws and limitations in non-mandated, non-label-seeking, phase-IV trials designed by commercial sponsors.

As discussed in Part III.E.i, what matters most is not whether one can prove that commercially-designed trials are statistically more likely to contain methodological bias than protocols created without industry influence, but whether pharmaceutical companies are sometimes given an incentive to utilize suboptimal research methods. One must keep this in mind if future research determines that industry sponsors are no more likely than disinterested academics to design inappropriately targeted protocols. Such a determination does not indicate the absence of a problem; it merely suggests that pharmaceutical companies tend to resolve their conflicts of interest by serving the public health instead of maximizing shareholder wealth.

¹⁸⁹ See *supra* note 40.

¹⁹⁰ See *supra* notes 28–35 and accompanying text (discussing the difference between methodological flaws and methodological limitations).

¹⁹¹ See, e.g., Bero & Rennie, *supra* note 14, at 216 (discussing nonrandom allocation of treatment); *id.* at 218 (discussing the unblinding of study subjects and/or researchers); see generally S. C. Lewis & C. P. Warlow, *How to Spot Bias and Other Potential Problems in Randomised Controlled Trials*, 75 J. NEUROL. NEUROSURG. PSYCHIATRY 181 (2004).

¹⁹² Lexchin et al., *Industry Sponsorship*, *supra* note 16, at 1170. See *supra* notes 28–35 and accompanying text for a discussion of how Lexchin et al.'s article addresses methodological flaws but fails to address methodological limitations.

Furthermore, a discovery that voluntary, industry-designed, non-label-seeking, post-approval protocols are no more likely than publicly financed trials created by non-conflicted academics to contain bias of any sort, does not entirely preclude the possibility that pharmaceutical companies intentionally design suboptimal studies. It may be the case that all studies employ suboptimal research methods. This is true for two reasons. First, many academics—even those who are financially disinterested—may have an incentive to design suboptimal trials that are more likely to yield positive results, since such studies may be more helpful in advancing an investigator's career.¹⁹³ Second, since pharmaceutical companies fund seventy percent of the clinical trials conducted in the United States,¹⁹⁴ they may be able to exert significant influence over what qualifies as the “gold standard.”¹⁹⁵ When designing a study, disinterested academics must draw on their collective knowledge of proper trial design, focusing specifically on the type of study and drug class at hand. This knowledge base has been created from the researchers' prior experience with clinical trials, of which approximately seventy percent were commercially-sponsored. It therefore seems reasonable to hypothesize that academics' collective understanding of trial design, and thus their ability to design perfect protocols, may be somewhat compromised by their overexposure to industry-funded studies.

If industry-sponsored trials indeed have a substantial effect on the definitions of various “gold standards” of research, it is even more important to align the profit incentives of commercial trial designers with the public health. Protocol design is as much an art as it is a science; there are no perfect trial designs, only those which are better or worse than their predecessors.¹⁹⁶ Even if pharmaceutical companies are no more likely than disinterested academics to concoct loaded research methods, trial designers should be given incentives to innovate. Eliminating the conflicts of interest inherent in the trial design process, without eradicating firms' fiduciary obligation to shareholders, would provide pharmaceutical sponsors with profit-based motiva-

¹⁹³ Although journal editors are equally likely to publish positive and negative results, researchers tend to assume that reports of negative results will be rejected. See generally Kay Dickersin et al., *Publication Bias and Clinical Trials*, 8 CONTROL. CLIN. TRIALS 343 (1987); Carin M. Olson, et. al., *Publication Bias in Editorial Decision Making*, 287 JAMA 2825 (2002).

¹⁹⁴ Mello et al., *supra* note 13, at 2202.

¹⁹⁵ The term “gold standard” refers to the most respected methodology that one can use to answer a specific research question.

¹⁹⁶ See Drummond Rennie, *Thyroid Storm*, 277 JAMA 1238, 1240 (1997).

tion to create new study designs that are more informative to the medical public.

IV. SOLVING THE PROBLEM: ALIGNING THE INCENTIVES OF INDUSTRY SPONSORS WITH THE PUBLIC HEALTH

A. *Preexisting Checks on Commercial Power—Why the Current Legal/Regulatory Regime Fails to Protect the Public from Methodological Limitations*

Before presenting solutions designed to remove pharmaceutical companies' incentives to design methodologically suboptimal trials, it is necessary to discuss five mechanisms within the current legal/regulatory landscape that, at least in theory, have the potential to curb such incentives. This section discusses the shortcomings of FDA oversight, physicians as informed agents, insurers' power to make coverage decisions, journal editors, and the tort system, ultimately concluding that they are unable to rein in conflicted trial designers.

(i) FDA Oversight—Can Government Regulators Remove Industry's Incentive to Design Methodologically Suboptimal Trials?

The FDA has the power under the Federal Food, Drug, and Cosmetic Act to prevent the dissemination of industry documents that are "false or misleading in any particular."¹⁹⁷ Although such authority suggests that the FDA has the ability to prevent pharmaceutical companies from utilizing suboptimal post-approval studies in their marketing efforts, regulators' real world capacity to do so is severely limited. This is true for three principal reasons.

First, the FDA is not able to conclusively demonstrate that suboptimal but unflawed protocols are substantially "false or misleading" to warrant regulatory action. Unlike the case with flaws, the presence or absence of a methodological limitation is dependent on the cost associated with improving the trial, and is thus always open to debate.¹⁹⁸ A protocol is suboptimal if and only if the benefits associated with the absent data outweigh the cost of making the results more informative to the prescribing public. Industry sponsors are always able to argue that six more months of data, more elderly patients, or a different comparator would have made the study prohibitively costly.

¹⁹⁷ 21 U.S.C. § 352(a) (2000).

¹⁹⁸ See *supra* notes 28–35.

Second, First Amendment concerns require the FDA to tread gingerly when regulating in this area. The First Amendment permits pharmaceutical companies to publish studies that the FDA considers false and misleading, as well as distribute them to physicians in response to unsolicited queries.¹⁹⁹ There is a thin line between actively promoting a product with allegedly false and misleading data, and merely providing such data to physicians who request it. The FDA must be careful not to disturb the sense of public legitimacy that is paramount to the smooth functioning of any administrative agency. Thus, when a company walks the line between what is constitutionally protected and statutorily condemned, the FDA is likely to err on the side of caution, permitting the firm to continue the arguably promotional activity until its behavior is unquestionably prohibited by law.²⁰⁰ Furthermore, even if industry consistently stayed well within the boundaries of the Federal Food, Drug, and Cosmetic Act, the mere existence of the biased data in medical journals and dissemination of the information to requesting physicians would likely exert significant influence over prescribers.

Finally, the FDA does not have the resources necessary to police firms' use of post-approval research, nor are the penalties levied by the FDA against disseminators of false and misleading data strict enough to deter improper industry behavior.²⁰¹ The FDA simply does not have the manpower needed to investigate complaints that competitors are using loaded research methods. Moreover, even if the FDA had the necessary resources, industry would likely still flout the law, as the typical penalty is nothing more than a warning letter. If the FDA had access to an army of reviewers and could credibly threaten criminal sanctions, trial designers might think twice before concocting suboptimal protocols.²⁰² Sadly, however, this is not the system in which the FDA operates.

¹⁹⁹ *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 67, 74–75 (D.D.C. 1998); Author's Personal Communication with Peter Hutt, Nov. 2005.

²⁰⁰ I do not suggest that the FDA flouts its duty to prosecute violations of the Federal Food, Drug, and Cosmetic Act. My point is merely that, in questionable cases, the FDA likely errs on the side of inaction.

²⁰¹ See James S. Benson, *State of the Food and Drug Administration*, 45 *FOOD DRUG COSM. L.J.* 301, 308 (1990); Teresa Moran Schwartz, *Punitive Damages and Regulated Products*, 42 *AM. U. L. REV.* 1335, 1344 n.51 (1993); Author's Personal Communication with Peter Hutt, Nov. 2005.

²⁰² Pharmaceutical companies might still publish what they believe to be appropriate, but refrain from distributing it.

(ii) Patients' Irrational Demand for Brand Name Drugs

Before examining the ability of physicians, insurers, journal editors and the tort system to reign in conflicted trial designers, it is necessary to discuss the tendency of patients to irrationally demand expensive, brand name medication when there are other, cheaper, safer and/or more effective therapies available. This section should not be taken to suggest that brand name drugs rarely offer a benefit over cheaper alternatives. To the contrary, newer medicines often present significant advantages over off-patent compounds and non-drug interventions. This section focuses on the minority of clinical situations in which an expensive, brand name medication is not the most cost-effective treatment.

Pharmaceutical companies spend approximately 2.5 billion dollars a year on direct-to-consumer (DTC) advertising.²⁰³ There is no doubt that DTC advertising increases sales.²⁰⁴ The only question is, what percentage of the consumers who receive a prescription as a result of DTC advertising receive better and more cost-effective care because of that prescription? This question is hotly debated,²⁰⁵ but a great deal of evidence suggests that much of the demand linked to DTC advertising is irrational from a societal standpoint.²⁰⁶ In other words, society would be better off if consumers used an alternative therapy instead of the advertised drug since the alternative therapy would be (a) safer and/or more effective for the patient, or (b) more cost-effective, which would mean that additional health care resources would be available for other patients.²⁰⁷ Such an argument, however, can be made for just about any product. Take automobiles

²⁰³ Meredith B. Rosenthal et al., *Promotion of Prescription Drugs to Consumers*, 346 *NEW ENG. J. MED.* 498, 498 (2002).

²⁰⁴ Abramson, *supra* note 45, at 158–59. After all, if such advertising did not increase sales by an amount that exceeded the cost of the advertisements, companies would cease to engage in DTC marketing.

²⁰⁵ Compare Sidney M. Wolfe, *Direct-to-Consumer Advertising—Education or Emotion Promotion?*, 346 *NEW ENG. J. MED.* 524 (2002), with Alan F. Holmer, *Direct-to-Consumer Advertising—Strengthening our Health Care System*, 346 *NEW ENG. J. MED.* 526 (2002).

²⁰⁶ See, e.g., Abramson, *supra* note 45, at 149–59 (discussing DTC advertising generally); *id.* at 258 (citing reports that “Celebrex and Vioxx, two drugs of very limited clinical value, have become blockbusters in the United States but not in the rest of the world [where DTC advertising is not permitted by the government]”). See ANGELL, *THE TRUTH*, *supra* note 21, at 125 (discussing how DTC advertisements are prohibited in all developed countries except for the United States and New Zealand).

²⁰⁷ The phrase “society would be better off” indicates that the sum of everyone’s individual levels of utility would be maximized by using alternative treatments. Such an idea takes into account the fact that one individual may gain more utility from curing a toenail fungus than another gains from treating her diabetes.

for example. BMW's marketing campaign may cause an individual to purchase the company's latest creation even though a "generic vehicle" is functionally superior²⁰⁸ or more cost-effective.²⁰⁹

There are three differences between the market for pharmaceuticals and the markets for other products that make the societally irrational demand in the latter more tolerable than in the former.²¹⁰

First, advertisements for items other than drugs have the potential to increase the value of the product to the consumer. One may obtain more utility from driving a BMW than a "generic car" not only because the BMW is functionally superior to the generic, but also because the company's marketing campaign has made the car's brand name synonymous with excellence and prestige.²¹¹ In other words, a BMW in a world without marketing would be less valuable to a consumer than the exact same vehicle in a society with automobile advertisements.²¹² It is unclear, however, whether the same is true for pharmacologic interventions. Although one could argue that DTC advertising enhances the placebo effect of brand name medication by making patients believe more strongly that the drug will work, the issue has never been tested.²¹³ Nor has it been determined whether consumers of advertised drugs derive utility from consciously or subconsciously believing that they are receiving the best treatment avail-

²⁰⁸ Functional superiority must be defined according to the consumer's preferences. For example, if an individual values a sound system much more than safety features, then a car with a state-of-the-art stereo may be considered functionally superior to a vehicle with \$20,000 worth of safety equipment but an average sound system.

²⁰⁹ In this sense, "cost-effective" is defined in terms of the financial cost per unit of utility provided by the automobile. Advertising may cause a consumer to purchase a \$50,000 BMW and receive 5000 units of utility from its use (\$10/unit) even though a generic car provides 4000 units of utility and costs \$20,000 (\$5/unit). It should be noted that the "societally irrational" consumer demand for drugs and cars is not necessarily irrational from the buyer's perspective. If an advertised drug is marginally more effective than a much cheaper generic, but the patient is wealthy and thus values the minute increase in effectiveness more than the twenty-five dollar difference in co-payments, the brand name medicine represents the personally rational choice. Similarly, although most people find that the functional superiority of a BMW over a "generic car" is incommensurate with the cost differential, wealthier individuals may value the marginal increase in quality more than its price.

²¹⁰ Hereinafter the phrase "irrational demand" signifies a demand that is irrational from the standpoint of society. When discussing what is rational from one's personal perspective, the word irrational is modified with an adverb such as "personally" or "individually."

²¹¹ See BMW Advertisements—Marketing the Ultimate Driving Machine, <http://www.bmwworld.com/ads/> (last visited Oct. 7, 2007).

²¹² This effect may be strong enough to render the demand for the vehicle no longer irrational.

²¹³ Author's Personal Communication with Bernard P. Schachtel, M.D., Aug. 31, 2005.

able.²¹⁴ In fact, it seems equally plausible (although this has never been tested either) that patients who ask for and receive an advertised drug from their doctors experience less of a placebo effect and are less confident that they are receiving optimal therapy than those who allow physicians to independently prescribe the appropriate remedy.²¹⁵ An individual who initiates a discussion about an advertised drug with her doctor may later question whether she influenced the doctor's decision to prescribe the medication, thereby reducing the patient's confidence in the drug's effectiveness.²¹⁶

Second, unbiased, *comparative* information that is understandable to the layman is almost impossible to come by for pharmaceuticals, but easy to obtain for other products.²¹⁷ Consumer Reports and J.D. Power and Associates release easy-to-digest evaluations and comparisons of virtually every car.²¹⁸ Thus, if an automobile advertisement erroneously convinces a consumer that a BMW offers her a lower price per unit of utility than a generic car, it is only because the buyer failed to sufficiently research her choices.²¹⁹ In the market for pharmaceuticals, however, there is a dearth of unbiased, comparative information with which consumers can investigate whether their desire for an advertised medicine is justified.²²⁰ As purchasing agents for their patients, physicians are supposed to fill the void by discussing the pros and cons of the advertised drug and alternative therapies.²²¹ The following section, however, demonstrates that physicians are often unable to adequately perform this task.²²²

Third, unlike the individuals who respond to advertisements in other industries, consumers who request an advertised medication almost always have some form of prescription drug coverage.²²³ The

²¹⁴ *Id.*

²¹⁵ *Id.*

²¹⁶ *Id.*

²¹⁷ David Lansky, *Providing Information to Consumers*, in CONSUMER-DRIVEN HEALTH CARE: IMPLICATIONS FOR PROVIDERS, PAYERS, AND POLICYMAKERS 419, 419–27 (Regina Herzlinger ed., 2004); J.D. Power III, *The Role of Information—J.D. Power's Paradigm Lessons from the Automotive Industry*, in CONSUMER-DRIVEN HEALTH CARE: IMPLICATIONS FOR PROVIDERS, PAYERS, AND POLICYMAKERS 410, 410–18 (Regina Herzlinger ed., 2004).

²¹⁸ See Consumer Reports, <http://www.consumerreports.org/main/home.jsp> (last visited Oct. 7, 2007); J. D. Power and Assocs., <http://www.jdpower.com/autos/> (last visited Oct. 7, 2007).

²¹⁹ See *supra* note 209 (discussing “price per unit of utility”).

²²⁰ See *infra* Part IV.C.iii.a (discussing proposals to establish an unbiased rating system for pharmaceuticals).

²²¹ Holmer, *supra* note 205.

²²² See *infra* Part IV.A.iii.

²²³ A recent survey determined that approximately seventy percent of the population has health insurance with prescription drug coverage. This number will likely

presence of insurance allows the patient to externalize much of the drug's cost onto the insurance company's other customers.²²⁴ A brand name, advertised medication may cost the insurer \$400 more per month than an alternative, generic compound, but to the consumer, the difference may be an extra \$25 co-payment. A patient who believes that the more expensive medication is worth \$50 more (or any amount greater than \$25) will seek out a prescription for the brand name drug, pay her copay and externalize the rest of the drug's cost onto her fellow insureds.

An informed individual shopping for health insurance has an incentive to select a plan that does not respond to the whims of consumers' irrational demand for brand name drugs. The intelligent shopper wishes to forego advertised medications when there are cheaper alternatives that are medically equivalent or negligibly inferior to the brand name drug, since, if all of the insurer's clients do so as well, she will secure a health plan with lower premiums. Unfortunately for such an enlightened consumer, insurance companies do not design their prescription drug benefit packages in a way that *adequately* combats consumers' irrational demand for brand name drugs.²²⁵

Although DTC advertising contributes significantly to consumers' irrational demand, its abolition would not cure the problem. Anecdotal reports from friends, or a general belief that newer medicines are generally better than older generics, may cause patients to request expensive drugs. The dearth of unbiased information discussing the pros and cons of different therapies would prevent consumers from determining which drugs are right for them. Finally, and most importantly, the externalities imposed by the current

rise as baby boomers age and begin to take advantage of Medicare's recent commitment to pay for medication. See Aflac, *Aflac Survey Reveals Disparities in Americans' Perceptions of Vision Health; More than Half of Respondents Report Having Vision Problems*, June 6, 2005, <http://www.aflac.com/us/en/aboutaflac/PressReleaseStory.aspx?rid=717509>. Due to the externalities inherent in medical insurance, it is likely that more than seventy percent of the patients requesting brand-name, advertised drugs from their doctor have prescription drug coverage. In other words, the group of requesting patients likely self-selects for consumers with prescription drug benefits.

²²⁴ See Jon D. Hanson & Kyle D. Logue, *The First-party Insurance Externality: An Economic Justification for Enterprise Liability*, 76 CORNELL L. REV. 129, 139 (1990) (discussing a similar point in the realm of liability insurance); see also Steven P. Croley & Jon D. Hanson, *What Liability Crisis? An Alternative Explanation for Recent Events in Products Liability*, 8 YALE J. ON REG. 1, 9 (1991). Although insurance companies' primary clients are most often employers, the phrase "other customers" represents the employees who obtain insurance through their employers and the individuals who purchase insurance directly from the insurance company.

²²⁵ See *infra* Part IV.A.iv.

health insurance climate would still lead consumers to seek out expensive drugs that are not cost effective.

(iii) Physicians—Can they Protect us from Methodological Bias by Altering their Prescribing Habits?

Industry advocates might argue that physicians are able to correct for any methodological bias in commercially-funded trials by altering their prescribing behavior accordingly.²²⁶ The argument goes as follows: Physicians serve as consumers' purchasing agents insofar as they usher patients toward the safest, most medically effective and most cost-effective therapy possible. Doctors are expected to review the medical literature and read published studies with a skeptical eye. If a physician reads a study that enrolled a disproportionate number of women, erroneously extrapolates the data to men, and prescribes the drug in question to both sexes without confirming the soundness of her extrapolation, then the doctor has failed her patient and the appropriate remedy is a lawsuit for malpractice.

There are four problems with the idea that physicians can reduce the incentive to design suboptimal trials by custom fitting their prescribing decisions to their perceptions of methodological limitations.

First, even if a physician recognizes all pertinent methodological limitations, much of the information needed to make sound prescribing decisions may not exist. In the case of study populations that are

²²⁶ See, e.g., Malcolm Gladwell, *High Prices—How to Think about Prescription Drugs*, THE NEW YORKER, Oct. 25, 2004, at 86. Gladwell discusses AstraZeneca's development of Nexium, attempting to combat the staunch criticism that the drug received from Marcia Angell in *The Truth about the Drug Companies*. See ANGELL, THE TRUTH, *supra* note 21, at 76–79. Although Gladwell fails to mention AstraZeneca's use of inappropriate comparators, he admits that the company spent half a billion dollars on advertising to “keep cheaper generics at bay.” Gladwell, *supra* note 226; see *supra* note 39 (discussing of how AstraZeneca used high doses of Nexium and low doses of a generic product in order to obtain favorable data). Gladwell goes on to write that

[o]f course, it is also the case that Nexium is a prescription drug: every person who takes Nexium was given the drug with the approval of a doctor—and doctors are professionals who ought to know that there are many cheaper ways to treat heartburn. If the patient was coming in for the first time, the doctor could have prescribed what's known as an H2 antagonist, such as a generic version of Tagamet (cimetidine), which works perfectly well for many people and costs only about twenty-eight dollars a month. If the patient wasn't responding to Tagamet, the doctor could have put him on the cheaper, generic form of Prilosec, omeprazole.

Gladwell, *supra* note 226, at 86. See also Rosenthal et al., *supra* note 200, at 502 (discussing how doctors only write prescriptions when they are “familiar with [the drug] and comfortable prescribing it.”).

unrepresentative of the patient population taking the drug, there will be some information available about all of the subpopulations for which the drug is approved, since the FDA requires such data for approval. Thus, if a study enrolled a disproportionate number of women and the drug is approved for use in men as well, a physician should be able to obtain the medication's safety and effectiveness profiles for both sexes from the package insert. With other types of methodological limitations, however, the prescriber may be unable to obtain the information she needs. For instance, if an industry-sponsored, head-to-head post-approval trial concludes that the company's brand name medication causes less adverse side effects than a generic competitor (an alternative, off-patent drug) in a subpopulation for which there is no FDA approval, a physician will not be able to tell if a longer study would have revealed additional side effects.²²⁷ Moreover, if the results were reported in terms of a broad class of side effects and data were not collected on the occurrence of individual side effects, physicians will not be able to determine if analyzing the different adverse effects individually would have yielded different results.²²⁸

Second, even if the relevant data were available, a comprehensive review of the medical literature pertaining to a popular drug class (e.g., statins or Cox-2 inhibitors) would be an impossible undertaking for a team of one hundred doctors, let alone a physician with a solo practice.²²⁹ If the desired data were collected during phase I–III trials, it is likely that the physician would not have to look further than the package insert. Relevant data collected in other non-required post-approval studies, however, would be far more difficult to track down. Medical providers do not have the time or expertise to systematically review clinical trials and evaluate their research methods.²³⁰ Physicians express extreme dissatisfaction with the amount of time that they must spend on administrative matters.²³¹ Additional responsibilities away from patient care will frustrate them further and shrink physicians' total compensation, thereby reducing the incentive

²²⁷ See *supra* Part III.E.ii.a (discussing how pharmaceutical companies may have an incentive to sponsor unduly short trials in order to conceal a drug's side effects).

²²⁸ See *supra* Part III.E.iv.c (discussing how pharmaceutical companies may have an incentive to inappropriately broaden or shrink categories of adverse side effects).

²²⁹ Jeremy Grimshaw et al., *Cluster Randomized Trials of Professional and Organizational Behavior Change Interventions in Health Care Settings*, 599 ANNALS AM. ACAD. POL. SOC. SCI. 71, 73 (2005) (discussing the potential for "information overload").

²³⁰ *Id.*

²³¹ Abigail Zuger, *Dissatisfaction with Medical Practice*, 350 NEW ENG. J. MED. 69, 71 (2004) (discussing administrative burdens associated with managed care).

for individuals to enter the medical profession. Primary care, an area that already has remarkable difficulty attracting qualified medical students,²³² is especially vulnerable to reduced physician satisfaction and compensation since doctors in this specialty prescribe a diverse array of medication. Even if time were not an issue, physicians lack the training necessary to analyze complex protocols.²³³ Many older doctors are not computer literate and have little understanding of the Internet.²³⁴ Given the discrepancy between doctors' current ability to critique the research methods of clinical trials and what is needed for them to make prescribing decisions based on their analyses, training physicians to understand the niceties of methodological limitations would likely be prohibitively costly.

Third, even if the data were available and physicians were capable of consistently spotting methodological limitations, marketing directed at physicians (including sales representatives) might be able to erroneously convince physicians that their assessments are flawed (and consumers' irrational demands are, in actuality, societally rational).²³⁵ Although doctors would be able to pool the biased information obtained from each firm's marketing efforts,²³⁶ companies that spend more hyping up their products would be more likely to influence prescribers.²³⁷ Generics, dietary supplements, and lifestyle modifications, all of which are much less marketed than brand name pharmaceuticals, would likely be underprescribed.²³⁸

Fourth, doctors have a financial interest in pleasing their patients. Physicians who have studied the medical literature and determined that the methodological limitations inherent in a company's post-approval trials render its drug medically inappropriate for a patient must combat the patient's irrational demand for the product. Suppose a provider determines that an alternative, generic drug

²³² See generally Ruth-Marie E. Fincher, *The Road Less Traveled—Attracting Students to Primary Care*, 351 NEW ENG. J. MED. 630 (2004); Michael E. Whitcomb & Jordan J. Cohen, *The Future of Primary Care Medicine*, 351 NEW ENG. J. MED. 710 (2004).

²³³ Grimshaw et al., *supra* note 229, at 73.

²³⁴ Jeffrey L. Drezner, *Understanding Adoption of New Technologies by Physicians*, MEDSCAPE.COM, Feb. 7, 2000, <http://www.medscape.com/viewarticle/408031>.

²³⁵ See, e.g., Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?*, 283 JAMA 373, 378 (2000).

²³⁶ Benjamin Falit, *The Path to Cheaper and Safer Drugs: Revamping the Pharmaceutical Industry in Light of GlaxoSmithKline's Settlement*, 33 J.L. MED. & ETHICS 174, 174–75 (2005) [hereinafter Falit, *Cheaper & Safer Drugs*] (citing T.A.M. Kramer, *A Plea for Biased Information*, MEDSCAPE.COM, Feb. 10, 2004, http://www.medscape.com/viewarticle/468112_1).

²³⁷ Lexchin, *Interactions*, *supra* note 139, at 64; Wazana, *supra* note 242, at 378–379.

²³⁸ Lexchin, *Interactions*, *supra* note 139, at 64.

would be equally as good as the brand name product in all respects, but costs \$300 less per month and is therefore the preferred course of treatment. An insured consumer afflicted with an irrational demand might respond that she would rather take the more expensive drug since the difference in co-payments is meaningless to her and several of her friends have responded well to it. If, after a thorough discussion of the pros and cons of each therapy, the doctor caves in to the patient's irrational request, the patient will be more likely to return to the provider's office for future care.²³⁹ A great deal of evidence suggests that physicians frequently accede to patients' socially irrational requests for brand name drugs in order to ease the strain on the doctor-patient relationship.²⁴⁰

(iv) Insurers—Can Coverage Decisions and Formularies
Protect us from Methodological Limitations?

One might contend that insurance companies should be able to correct any methodological bias (thereby providing pharmaceutical companies with an incentive to design optimal trials) by designing drug benefit packages that selectively reimburse the appropriate medications.²⁴¹ There are four problems with such an assertion.

First, as is the case with physicians' ability to curb methodological bias, the information necessary to make informed decisions about the best therapy for each patient may not exist.²⁴² In order to accurately assess the quality of prescription drugs, health plans would have to redo the industry-sponsored studies with more informative research methods. For instance, an insurer might collect data on more narrow categories of side effects or run the study for a longer period of time.²⁴³ Insurers are unwilling to engage in such research, not only because the cost of such trials might outstrip any savings associated with the use of more cost-effective medicine, but also because other health plans could free-ride off of their investments.²⁴⁴

²³⁹ Abramson, *supra* note 45, at 156.

²⁴⁰ See, e.g., *id.* at 155–57 (speaking to “[d]isempowering the doctor-patient relationship”).

²⁴¹ See Gladwell, *supra* note 226, at 89.

²⁴² See *supra* notes 227–28 and accompanying text.

²⁴³ See *supra* Parts III.E.ii, iv (discussing how industry sponsors may have an incentive to inappropriately broaden or narrow categories of adverse events or design a trial that is shorter than what the public desires).

²⁴⁴ Hanson & Logue, *supra* note 224, at 149. Even if competitors could not free-ride (and hence all conducted their own trials), the fact that a trial's cost outstrips the savings that will inure to the insurer does not suggest that society would not benefit from conducting the trial. It may be the case that the benefits will outweigh

Since the data generated by the insurer-sponsored clinical trials cannot be protected by intellectual property law,²⁴⁵ health plans are unable to reap the full return on their investments.²⁴⁶ Free-riding competitors who are able to utilize the information without incurring any of the costs associated with producing it would be able to offer insureds comparatively low premiums.²⁴⁷ Collectively, insurers have an incentive to conduct additional trials in order to determine which therapies are the most cost effective, but individually each health plan has an incentive to wait until the task is undertaken by a competitor and gain a comparative advantage by free-riding off of its investment. The result is a system in which insurers do not sponsor clinical trials.²⁴⁸

Second, medicine is as much an art as it is a science. Insurance companies who want to treat their customers as cost-effectively as possible cannot simply mandate one-size-fits-all, cookbook remedies.²⁴⁹

the costs only if economies of scale can be exploited, i.e., only if the data can be used to shape reimbursement for more insureds.

²⁴⁵ State St. Bank & Trust Co. v. Signature Fin. Group, Inc., 149 F.3d 1368, 1373 (Fed. Cir. 1998) (noting that raw information is not patentable). The inability to protect the data produced by one's research via intellectual property law is an important issue in research sponsored by pharmaceutical companies. The pharmaceutical industry has fought hard to make sure that clinical trial registration requirements do not reduce the incentive to invest in research by allowing competitors to free-ride off of the sponsoring company's investment. See Benjamin Falit, *Pharma's Commitment to Maintaining a Clinical Trial Register: Increased Transparency or Contrived Public Appeasement?*, 33 J.L. MED. & ETHICS 391 (2005) [hereinafter Falit, *Pharma's Commitment*].

²⁴⁶ Hanson & Logue, *supra* note 224, at 149.

²⁴⁷ *Id.*

²⁴⁸ If insurers joined together to sponsor clinical trials and reimbursed only the most cost effective therapies, pharmaceutical companies would no longer have an incentive to design methodologically suboptimal trials, since doing so would not make a health plan any more likely to pay for the sponsor's drug. Since pharmaceutical companies would no longer design suboptimal protocols, the insurers would have very few studies to redo (although they still might choose to conduct their own research). In essence, insurers' *ability* to selectively reimburse only the best drugs by conducting their own research would likely be sufficient to reduce pharmaceutical companies' incentives to design methodologically suboptimal studies; the insurers would not have to actually perform such research. Nevertheless, the remainder of Part IV.A.iv demonstrates that insurers' capacity to sponsor clinical trials, by itself, would likely be insufficient to enable the selective reimbursement of the most cost effective drugs for all patients.

²⁴⁹ Regina Herzlinger, *Uncle Sam is No Doctor—Instead of Tracking Outcomes, System Prescribes Medical "Recipes"*, USA TODAY, Mar. 28, 2005, at 10A. The point is not that medical practice guidelines and evidence based medicine are deleterious, but rather that cost effective care requires *some amount* of individualization. This is likely to be especially true in the future as developments are made in the field of pharmacogenomics. Pharmaceutical companies would be hard pressed to argue that personalization need not play a role in cost-effective care. One of the industry's primary arguments for why the production of me-too (follow-on) drugs are beneficial to society,

In some cases, a brand name drug that is generally no more efficacious than cheaper alternatives will prove to be the medically appropriate and most cost effective therapy. In other words, it's extremely difficult, if not impossible, for insurers to design benefit packages that reimburse only the most cost-effective care in all cases.²⁵⁰ Health insurers are forced to reimburse care that will often be inappropriate from society's standpoint, and provide physicians with incentives to use the most cost-effective care.²⁵¹ The collective action and free-rider problems discussed in relation to insurer-sponsored clinical trials apply to the implementation of innovative reimbursement mechanisms as well. Insurers' ability to invest in the development of a prescription drug benefits program able to selectively reimburse the most cost-effective care for all patients, is stifled by competitors' ability to costlessly replicate the innovative policy.²⁵²

Third, the political backlash against managed care has demonstrated that physicians and health care consumers desire empowerment.²⁵³ Patients want to play an integral role in their own care and doctors do not want to be second-guessed by corporate bureaucrats. Just like physicians, payers have an incentive to please their customers so that they continue supplying the company with business. An insurance company that attempts to wage war against consumers' demands for brand name medications with seemingly despotic formularies may lose business to competitors that cater to the insureds' irrational requests. Since drugs that are generally not cost-effective may be appropriate for some patients, refusals to cover the drugs when doctors accede to patients' requests pit the insurance company

has been that some individuals may respond poorly to one drug in a class but respond well to a me-too product in the same class. See DiMasi & Paquette, *supra* note 175, at 11–12 (discussing this argument).

²⁵⁰ In theory, it is possible to design a system where medical reviewers employed by an insurance company review all brand-name prescriptions or prescriptions for drugs that tend to generate an irrational demand in consumers. Although such a system might enable an insurer to reimburse only the most cost-effective drugs, acquiring and analyzing the information necessary to make an informed decision in every case would likely be prohibitively costly.

²⁵¹ Insurers often use capitation and pay-for-performance mechanisms to provide physicians with a financial incentive to render cost effective care. See Capitation—A List of Articles from Managed Care Magazine, <http://www.managedcaremag.com/capitation.html> (last visited Oct. 7, 2007) (list of articles discussing capitation); Am. Med. Assoc., Guidelines for Pay-for-Performance Programs, <http://www.ama-assn.org/ama1/pub/upload/mm/368/guidelines4pay62705.pdf> (last visited Oct. 7, 2007).

²⁵² Hanson & Logue, *supra* note 224, at 149.

²⁵³ Regina Herzlinger, *The Frayed Safety Net*, in CONSUMER-DRIVEN HEALTH CARE: IMPLICATIONS FOR PROVIDERS, PAYERS, & POLICYMAKERS 28, 46 (Regina Herzlinger ed., 2004) [hereinafter Herzlinger, *The Frayed Safety Net*].

against the doctor. Patients are likely to see the insurer's coverage refusals as self-serving, profit-maximizing devices and, if given a choice by their employer, may seek alternative health insurance.²⁵⁴

Collective action and free-rider problems also apply in the context of battling irrational requests for drugs. Individually, each payer lacks the incentive to educate its enrollees on the cost savings (via premium reductions) associated with collectively agreeing to utilize the most cost-effective therapy, since consumers frequently change insurance companies.²⁵⁵ If insurer A invests in combating its customers' irrational demand, insurer B, who later insures these newly-enlightened individuals, is able to free-ride off of A's investment by costlessly obtaining societally rational consumers. The money insurer B saves by not educating its enrollees allows it to offer lower premiums that attract more customers. The result is that no payers are willing to combat their customers' irrational demands with education.

Fourth, since consumers frequently change employers (and thereby change insurers), insurance companies have little incentive to design innovative plans which encourage beneficiaries to seek high-quality care that is cost-effective over the *long term*. Instead, each firm has a perverse incentive to minimize short-term costs (the cost of care during the period in which a patient is likely to remain insured by the company). If the focus on short-term expenditures increases the overall cost to the system because more expensive care is needed later in life, then it is of no concern to the company, since the later costs are borne by the patient's new insurer. In other words, payers individually desire an imperfect market for health care services in which patients have neither the knowledge nor the incentive to make rational purchasing decisions. Insurers prefer to implement supply-side techniques that actively manage overuse but fail to correct for underuse that does not result in *short term* cost increases. For example, suppose that there are two, equally effective and equally safe medical treatments for a particular ailment. The infirmity can be corrected with a one-time surgery that will cost the insurance company \$5000 or with medication that must be administered for the patient's lifetime, which will cost \$1000 per year. From a societal standpoint, surgery is the best option if the patient is expected to live more than five years, since this is the point at which the drug costs exceed the cost of the one-time operation. The insurer, however, has a different perspective. Even if the patient is expected to live for another

²⁵⁴ *Id.* at 46.

²⁵⁵ *Id.* at 32, 44.

sixty years, if the insurer expects that the enrollee will change insurance companies within the next five years, it may rationally choose to selectively reimburse the drug (refusing to reimburse the surgery). The patient's next insurer may do the same, and so on down the line.

(v) Journal Editors—Can they Protect the Public from Methodological Limitations by Selectively Publishing Soundly Designed Trials?

The medical profession's peer review system plays an incredibly valuable role in ensuring that only methodologically sound, correctly reported research is published and disseminated to physicians. The system, however, is not perfect. Journal editors, like physicians and insurance companies, are limited in their ability to curb methodologically suboptimal, industry-sponsored phase IV trials. This is true for three principal reasons.

First, methodologically flawless but suboptimal trials produce valid data.²⁵⁶ In order for a doctor to be misled by a study that is merely suboptimal, she must erroneously extrapolate the data to a situation not spoken to by the targeted protocol. For instance, if a six-month study determines that a brand name drug is safer than an alternative generic compound, a doctor who prescribes the medication for longer than six months on the basis of those results is inappropriately assuming that the brand name pharmaceutical will continue to outperform the generic. Were it not for physicians' tendency to improperly extrapolate from limited data, suboptimal yet flawless trials could not harm the public.²⁵⁷ Therefore, it might be argued that journal editors' decisions not to publish suboptimal but flawless trials would be tantamount to disempowering astute prescribers who do not inappropriately extrapolate from such studies in order to protect the patients of less perspicacious physicians. Journal editors are unwilling to withstand the attacks from patients, sponsors, and physicians that would inevitably accompany such paternalistic behavior. Rather than rejecting a methodologically flawless but suboptimal trial, editors prefer to ensure that the results are accurately reported. As discussed above in Part III.E.vi, full disclosure does not eliminate the problem associated with improperly targeted research. Suboptimal protocols deprive consumers and prescribers of important knowledge, regardless of whether the studies openly ac-

²⁵⁶ See *supra* notes 28–35 and accompanying text (discussing the difference between methodological limitations and methodological flaws).

²⁵⁷ See *supra* Part III.E.vi (noting that suboptimal protocols would still fail to maximally inform medical providers).

knowledge that the information is limited. Furthermore, even with accurate reporting, busy physicians who rely on pharmaceutical representatives for information and fail to read studies in their entirety may be prone to erroneously extrapolating from the limited data.

Second, from a physician's perspective, all trials are suboptimal to an extent since additional information (e.g., a longer study, data on additional subpopulations, etc.) is always helpful. From society's perspective, however, a protocol is suboptimal if and only if the benefits associated with the absent data outweigh the cost of making the results more informative to prescribers. It would be nearly impossible for journal editors to determine which trials are societally suboptimal. Industry sponsors will always be able to argue that six more months of data would have made the study prohibitively costly, and journal editors do not have the resources to conduct cost-benefit analyses on every publication. Indeed, it would likely be impossible for any individual or group of individuals to differentiate between legitimate targeted research and methodological limitations. It is for this reason that Part IV(C) advocates a system that uses the market, rather than technocrats, to police industry trial designers.²⁵⁸

Finally, pharmaceutical companies can still use unpublished post-approval trials to influence physicians' prescribing behavior. Although studies published in prestigious medical journals are more likely to sway doctors,²⁵⁹ pharmaceutical representatives often disseminate the results of unpublished phase IV trials to physicians.²⁶⁰ Although there is no evidence to suggest that the unpublished data has an effect on prescribing behavior, pharmaceutical companies are for-profit enterprises that would surely abandon the practice if it did not have a positive effect on sales.

(vi) The Tort System's Inability to Adequately Deter the
Creation of Methodologically Suboptimal Protocols

Product liability laws undoubtedly affect industry behavior. The threat of class action litigation helps to ensure that protocols are sound, research is conducted ethically, and results are accurately reported. The system, however, is not perfect. Like the FDA, physi-

²⁵⁸ See *supra* Part IV.C.iii.b.

²⁵⁹ *Medical Journals Act to Limit Drug Firms' Influence*, CNN.COM/HEALTH, Sep. 10, 2003, <http://archives.cnn.com/2001/HEALTH/09/09/journals.drugfirms/> (last visited October 7, 2007).

²⁶⁰ The dissemination of entirely unpublished data is rare, but industry often makes use of trade journals that are not peer reviewed. It is important to note, however, that industry is not permitted to distribute data on off-label uses. See *Washington Legal Found.*, 13 F. Supp. 2d at 73.

cians, insurers and journal editors, the tort system inadequately deters the design of methodologically suboptimal, non-required, non-label-seeking, post-approval protocols. A thorough discussion of this point would necessitate hundreds of pages and is thus beyond the scope of this Article. It is important, however, to briefly mention the four principal reasons for the tort system's inability to optimally constrain industry behavior.

First, it would be extraordinarily difficult and costly for a plaintiff to prove that an unflawed (but suboptimal) trial was negligently designed. In order to do so, one would have to demonstrate that the omitted information possesses a benefit to prescribers that outweighs the cost of producing the data.²⁶¹ In other words, in order to prevail at trial, the plaintiff must be able to attribute a dollar value to the harm caused by the suboptimal protocol that exceeds what it would have cost to rectify the limitation. Pharmaceutical companies can argue that alternative trial designs were financially impractical insofar as additional expenditures would have caused the firm's management to forego the trial entirely. Sponsors may contend that a longer trial was impossible since patients would have been unlikely to consent to extended participation in the study. In essence, study design does not lend itself well to ex post cost-benefit analyses of alternative protocols since it is inextricably intertwined with the inherently variable and unpredictable process of enrolling human subjects who consent to the trial's parameters. In cases in which the defendant's behavior was entirely legitimate with the exception of allegedly suboptimal protocols, plaintiffs will have a hard time overcoming the argument that alternative trial designs might have compromised subject enrollment, thereby jeopardizing the ability to collect any data whatsoever.

Second, even if it were always possible for plaintiffs to prove negligence to a jury's satisfaction, many suboptimal trials would still go undiscovered. In order to conclude that the methodology of a given protocol is suboptimal, one must have access to data from other trials which fill in the informational gaps left by the methodologically suboptimal study. For instance, imagine a pharmaceutical company sponsors a six-month trial that concludes that their brand name drug

²⁶¹ Although a plaintiff could succeed by arguing that the sponsor intentionally or recklessly designed the suboptimal trial, a claim of negligence would be the easiest hurdle to clear. Courts will often determine the presence or absence of negligence by applying a formula developed by Judge Learned Hand, in which the cost of an un-taken precaution is weighed against the costs of the injuries the precaution prevents. See *United States v. Carroll Towing Co.*, 159 F.2d 169, 173 (2d Cir. 1947).

is safer and more effective than an alternative generic compound in a subpopulation for which there is no FDA approval. There is no way for one to determine whether the study is inappropriately short without a subsequent trial that compares the two compounds for a longer duration. If the public sector fails to sponsor a longer study, patients taking the brand name drug will not be able to discern whether they are victims of negligently-designed trials.

Third, even if all methodologically suboptimal trials could be identified and plaintiffs were always able to prove that the studies were negligently designed, it would be exceedingly difficult to prove causation. In order to recover damages for their losses, plaintiffs must establish the existence of a causal connection between the defendant's allegedly tortious conduct and the injuries for which recovery is sought.²⁶² For instance, imagine a pharmaceutical company designed a suboptimal trial that misled patients and physicians into believing that a brand name drug was more effective than a generic alternative, even though the only difference between the two was price. An attorney bringing a class action suit on behalf of the consumers who took the brand name drug to recover the difference in cost would have to demonstrate that but for the suboptimally designed trial, the alleged victims would have foregone the brand name medication in favor of less expensive therapy. Pharmaceutical companies would be able to argue that, had the trial yielded less favorable results, the company would not have used sales representatives to disseminate the data. Without detail personnel alerting doctors to the results, physicians would have been less likely to use the data when writing prescriptions. Furthermore, sponsors would contend that, even if physicians were fully aware that cost was the only differentiating factor between the drugs, it is unlikely that they could have overcome patients' demand for brand name drugs. In essence, the burden is on the plaintiff class to prove that the absence of a methodologically suboptimal trial would have caused (a) the physician to suggest an alternative remedy and (b) the patient to accept the prescriber's recommendation. Given the speculative nature of such inquiries, establishing causation is likely to be a formidable obstacle for any plaintiff class.

²⁶² Guido Calabresi, *Concerning Cause and the Law of Torts: An Essay for Harry Kalven, Jr.*, 43 U. CHI. L. REV. 69, 73-91 (1975); Wex S. Malone, *Ruminations on Cause-In-Fact*, 9 STAN. L. REV. 60, 66-68 (1956); David Rosenberg, *The Causal Connection in Mass Exposure Cases: A "Public Law" Vision of the Tort System*, 97 HARV. L. REV. 851, 855 (1984) [hereinafter Rosenberg, *Causal Connection*] (citing H.L.A. HART & A. HONORE, CAUSATION IN THE LAW 64-76 (1959)).

Finally, the tort system is designed in such a way that defendant companies litigating large scale tort claims have an advantage over disaggregated plaintiffs. Since the defendant remains constant in all cases, it can take advantage of economies of scale to an extent that the various classes of plaintiffs cannot.²⁶³ In any suit, each party invests in the litigation up until the point where the expected return of the investment no longer exceeds its cost.²⁶⁴ The stakes are higher for the defendant than any incomplete plaintiff class²⁶⁵ since the defendant, unlike the plaintiffs, must litigate the same issues in trials brought by other alleged victims.²⁶⁶ Thus, the defendant will rationally invest more than its adversaries, making full compensation for the plaintiffs' injuries unlikely.²⁶⁷

B. Solutions Offered by Other Authors

Recognizing that the current legal/regulatory regime is incapable of exerting sufficient pressure on industry sponsors to eliminate methodological limitations, several authors have proposed reforms to the process of designing clinical protocols.

Bero and Rennie argue that pharmaceutical companies have a moral duty to design trials that best serve the public health and thus should unilaterally eliminate methodological bias.²⁶⁸ Sponsors of clinical trials, however, arguably have a *legal* duty to maximize shareholder wealth, even if such wealth maximization comes at the price of harming the public health.²⁶⁹ At the very least, pharmaceutical companies are forced to serve two diametrically opposed masters and therefore must choose between rewarding investors who have put their faith in the firm and attending to the needs of non-shareholder

²⁶³ Rosenberg, *Causal Connection*, *supra* note 262, at 902; David Rosenberg, *Response: Mandatory-Litigation Class Action: The Only Option for Mass Tort Cases*, 115 HARV. L. REV. 831, 852–53 (2002) [hereinafter Rosenberg, *Mandatory-Litigation*].

²⁶⁴ Rosenberg, *Mandatory-Litigation*, *supra* note 263, at 848–49. It is generally believed that plaintiffs' attorneys calculate the proper investment based on their expected payout. Assuming a one-third contingency fee structure, the attorney for a plaintiff class will continue investing time and money into a trial as long as the expected judgment increases by more than three times the amount required to produce it. *See id.* at 889–890 (discussing in detail the manner in which plaintiffs' attorneys determine optimal levels of investment in class action litigation).

²⁶⁵ The term "incomplete plaintiff class" signifies that some victims are not included in the class.

²⁶⁶ *See* Rosenberg, *Causal Connection*, *supra* note 262, at 848–49; Rosenberg, *Mandatory-Litigation*, *supra* note 263, at 902.

²⁶⁷ *See* Rosenberg, *Causal Connection*, *supra* note 262, at 852–53; Rosenberg, *Mandatory-Litigation*, *supra* note 263, at 903.

²⁶⁸ Bero & Rennie, *supra* note 14, at 229.

²⁶⁹ *See supra* Part II.B.

constituencies.²⁷⁰ Bero and Rennie argue that this dilemma is easily resolved in favor of the public health but, as discussed in Part II.B, courts and legal scholars do not agree.²⁷¹

Angell has called for the creation of an independent public body with the authority to design and administer clinical trials. She writes:

Drug companies would be required to contribute a percentage of revenues to this institute, but their contributions would not be related to particular drugs The institute would then contract with independent researchers in academic medical centers to conduct drug trials. The researchers would design the trials, analyze the data, write the papers, and decide about publication.²⁷²

Angell does not specify whether the pharmaceutical companies would still be permitted to fund and conduct clinical trials outside of the agency's control or, if so, whether the FDA would consider such studies for approval decisions.²⁷³ From a constitutional perspective, however, the answers to these questions are of paramount importance. If pharmaceutical companies were prevented from conducting independent research or were financially penalized for doing so, the general First Amendment right to pursue knowledge would likely destine the regime for failure.²⁷⁴ Congress or the FDA could constitu-

²⁷⁰ *Id.*

²⁷¹ See Elhaage, *supra* note 8, at 733 n.1. Bero and Rennie recognize that moral compulsion is insufficient to prompt the design of trials in which competitor products are used as comparators. Bero & Rennie, *supra* note 14, at 229. They propose two, alternative regulatory remedies to deal with the issue. First, they argue for the collection of a "user fee" from pharmaceutical companies that is used to fund studies of comparative effectiveness. *Id.* Due to the similarity between this proposal and those advocated by Angell and Abramson, a discussion of it is deferred until later in this section, where the solutions proffered by those authors are introduced. *Id.* Second, Bero and Rennie suggest that "data comparing new drugs with available alternatives for effectiveness and cost be added as an additional requirement for drug approval." *Id.* Such a regime is likely to be counterproductive since placebo-controlled studies are significantly less expensive than those using pharmacologic interventions as comparators, and in some cases, the marginal advancement in medical knowledge created by the head-to-head trial may not justify the decline in research that follows from the increased cost of conducting clinical trials. See *supra* Part III.E.v.a.

²⁷² ANGELL, THE TRUTH, *supra* note 21, at 245.

²⁷³ It is also unclear whether, under Angell's proposal, industry-funded and industry-designed phase IV trials could serve as the post-marketing evidence of safety and/or efficacy often required by the FDA for the drug to stay on the market.

²⁷⁴ *Griswold v. Connecticut*, 381 U.S. 479, 482-83 (1965). The Court discussed the unifying principle undergirding prior case law:

By *Pierce v. Society of Sisters* the right to educate one's children as one chooses is made applicable to the States by the force of the First and Fourteenth Amendments. By *Meyer v. Nebraska* the same dignity is given the right to study the German language in a private school. In other words, the State may not, consistently with the spirit of the First

tionally stipulate that only those trials conducted through the new federal body will be considered for approval decisions,²⁷⁵ but such a system would fail to curb methodological bias in non-mandatory, non-label-seeking phase IV trials.²⁷⁶

Abramson's proposal is similar to Angell's but avoids the thorny constitutional issues. He too advocates for the creation of an independent public body, stating that the newly-created agency would "have the power to require that studies include people of similar age, gender and medical condition to those to whom the results would be applied . . . [and] that studies be continued long enough to determine the benefits and side effects of the various treatments."²⁷⁷ Unlike Angell, however, Abramson stipulates that the pharmaceutical companies would still be permitted to conduct research on their own, without oversight from the federal body. Under his proposal, the agency's only power to enforce its requirements of methodological purity would lie in its ability to certify research as valid or invalid.²⁷⁸ Thus, in order for the oversight committee to be effective, physicians would have to be convinced that all "unapproved research" is not worthy of their attention. If physicians still take such research into account when writing prescriptions, the incentive to design methodologically suboptimal trials will remain even though such studies are not eligible for governmental certification.

Although Abramson's proposal might reduce the number of methodological limitations as well as their egregiousness, it is likely that other solutions would yield a more favorable cost-benefit trade-

Amendment, contract the spectrum of available knowledge. The right of freedom of speech and press includes not only the right to utter or to print, but the right to distribute, the right to receive, the right to read and freedom of inquiry, freedom of thought, and freedom to teach—indeed the freedom of the entire university community. Without those peripheral rights the specific rights would be less secure. And so we reaffirm the principle of the *Pierce* and the *Meyer* cases.

Id. at 482 (citations omitted).

²⁷⁵ Author's Personal Communication with Laurence Tribe, Mar. 15, 2005.

²⁷⁶ See *supra* note 61. Given the FDA's general failure to ensure the conduction of mandatory post-approval studies it is questionable whether such a regime would reduce the extent of methodological bias in FDA-required phase IV trials.

²⁷⁷ ABRAMSON, *supra* note 45, at 251. It is unclear why Abramson advocates for a new governmental body, rather than expanding the FDA. As the FDA commands significant respect from the public and the decisions of any new body would have to be reconciled with the FDA anyway, it seems foolish to create an entirely new governmental entity.

²⁷⁸ *Id.* at 252.

off.²⁷⁹ Pharmaceutical companies will expend vast amounts of resources defending their territory.²⁸⁰ They will argue that the enrollment of patients who consent to a trial's parameters is an inherently variable and unpredictable process that should not be second-guessed by centralized planners distanced from the sponsor's business concerns. If enrolling subjects and securing their consent to remain in the trial is sufficiently expensive, it may be in the public's interest to conduct a shorter study or use a patient population that is only somewhat representative of the individuals receiving the drug in the real world. Industry sponsors will contend that, if they are forced to obey the oversight committee, valuable research will go undone since the more costly studies demanded by the agency will be unjustifiable from a business perspective. Given inertial forces and the inevitable industry backlash, the agency may have difficulty establishing a brand name that commands enough respect to alter physician behavior.²⁸¹

Unlike the case with methodological flaws, the presence or absence of a methodological limitation is always open to debate.²⁸² A flaw produces invalid data that can be translated into improper treatment without any further error on the part of the physician. A limitation, however, is only dangerous if the prescriber extrapolates inappropriately from the information.²⁸³ Centralized government oversight of methodological flaws is less problematic than the management of limitations since the existence of the former, but not the latter, can be concretely proven by the oversight committee. Since cost considerations always arise when one evaluates a methodological

²⁷⁹ Abramson's proposal can be criticized for essentially maintaining the status quo. The FDA currently has the power to enforce its requirements of methodological purity by certifying non-required post-approval protocols as valid or invalid. However, limited resources restrict the FDA's ability to police all post-marketing research. See *supra* Part IV.A.i. Abramson's proposal therefore seems like nothing more than a recommendation to increase funding to the FDA so that it can review non-required phase IV results.

²⁸⁰ These costs must be taken into account when one calculates the price tag attached to the creation of a federal oversight committee.

²⁸¹ Moreover, as Abramson notes, the federal body would be a primary target for industry capture. ABRAMSON, *supra* note 45, at 250. Insulating the committee from private interests would be a difficult and costly process that must be considered when calculating the cost-benefit trade-off associated with the establishment of the agency.

²⁸² See *supra* notes 28–35 and accompanying text.

²⁸³ An example of improper extrapolation might be failing to recognize that the study enrolled predominantly women and applying the results to alter the treatment of a male patient.

limitation,²⁸⁴ the optimal mechanism for preventing methodological limitations is to provide industry sponsors with a profit incentive to design unbiased trials.

C. *Designing a New Solution*

(i) Supply-side vs. Demand-side Solutions—A Macro Level Perspective

On the macro level, the problem of methodological limitations can be approached in two ways. First, one can devise a supply-side intervention that acts directly on the industry sponsors, subjecting the design of clinical trials to continuous public scrutiny or mandating that protocols are created according to certain well-defined parameters. Angell's suggestion that "[d]rug companies should no longer be permitted to control the clinical testing of their own drugs" is an example of such a solution.²⁸⁵ Alternatively, one can devise a demand-side intervention that uses market forces to sculpt industry behavior. Abramson's proposal can be understood as a demand-side solution since its success depends on reduced physician demand (i.e., decreased willingness to write prescriptions) for drugs whose ostensible benefit is demonstrated predominantly by governmentally-uncertified clinical trials.²⁸⁶

Demand-side interventions that seek to curb methodological bias via physician prescribing habits are likely to be superior to supply-side solutions for three reasons. First, as discussed above with regard to Angell's proposal, regimes that act directly on pharmaceutical companies are likely to be unconstitutional.²⁸⁷ Second, the centralized planning/oversight inherent in supply-side solutions is inapt at ferreting out only those methodological limitations which are not justified by sponsors' cost considerations.²⁸⁸ Finally, demand-side interventions raise fewer concerns of corruption and agency capture, and are thus more likely to be viewed as legitimate by the public. For ex-

²⁸⁴ For example, one must determine whether the cost of enrolling more representative patients is justified by the marginal increase in information provided by the study.

²⁸⁵ ANGELL, *THE TRUTH*, *supra* note 21, at 244.

²⁸⁶ "Governmentally uncertified" studies are those that, even if approved by the FDA, did not receive approval from the new, federal body in charge of overseeing the design of clinical trials.

²⁸⁷ See *supra* notes 272–76 and accompanying text.

²⁸⁸ See *supra* notes 28–35 and accompanying text (providing a more thorough discussion of why the presence of methodological limitations—but not flaws—depends on sponsors' cost structure).

ample, the governmental committee proposed by Abramson is less vulnerable to industry influence than that proffered by Angell, since the success of the former, but not the latter, depends on doctors' widespread belief that the federal body overseeing the design of clinical trials is able to consistently (and without bias) distinguish between methodologically sound and unsound trials. Under Abramson's demand-side regime, if doctors suspect that the oversight committee has been corrupted by corporate influence, they will strip it of its power by ceasing to value its certification decisions.²⁸⁹

(ii) Supply-side versus Demand-side Solutions—A Micro Level Perspective

Within the realm of solutions that purport to curb methodological bias by altering prescribers' behavior, one must make a micro level choice of whether to use a supply-side or a demand-side intervention. Supply-side proposals are those that act directly on doctors without altering patients' demand for more appropriate prescribing.²⁹⁰ For instance, Soumerai and Avorn have suggested that the government comparatively evaluate various therapies, hire detail personnel, and employ the same techniques used by pharmaceutical sales representatives to decrease societally irrational prescribing.²⁹¹ Demand-side interventions are those that utilize the market for physician services to effectuate change. For example, in 1989, the New York State Department of Health developed a Cardiac Surgery Reporting System (CSRS) that collected and tracked clinical data on all cardiac surgeries performed in New York hospitals.²⁹² The Department of Health hoped that, by issuing annual report cards containing risk-adjusted mortality and complication rates for both hospitals and

²⁸⁹ Physicians' power to effectively override the oversight committee's certification decisions is a double-edged sword insofar as industry sponsors may be able to erroneously convince prescribers that the agency's determinations are flawed. *See supra* Part IV.B.

²⁹⁰ *See* Richard M. J. Bohmer, *Changing Physician Behavior* (Harv. Bus. Sch. Case No. 9-699-124, Mar. 22, 2000) (offering an excellent discussion of the mechanisms through which physician behavior can be influenced).

²⁹¹ *See* Stephen B. Soumerai & Jerry Avorn, *Principles of Educational Outreach (Academic Detailing) to Improve Clinical Decision Making*, 263 JAMA 549 (1990). Although studies have found such "academic detailing" to be successful at changing prescribers' behavior, it is enormously resource intensive. *See* Bohmer, *supra* note 290, at 21; Stephen B. Soumerai & Jerry Avorn, *Economic and Policy Analysis of University-based Drug "Detailing"*, 24 MED. CARE 313, 322 (1986).

²⁹² Richard M. J. Bohmer et al., *Bridges to Excellence: Bringing Quality Health Care to Life* (Harv. Bus. Sch. Case No. 9-604-030, Jan. 20, 2005); Regina E. Herzlinger & Seth Bokser, *Note on Accountability in the U.S. Health Care System* (Harv. Bus. Sch. Case No. 9-302-007, Aug. 19, 2004).

individual physicians, consumers' desire to be treated by a top performer would put pressure on surgeons to improve the quality of care.²⁹³

As was the case at the macro level, demand-side initiatives at the micro level are likely to be more effective than supply-side solutions. This is true for two reasons. First, only demand-side interventions are capable of aligning the interests of all three contributors to the ultimate health care decision—the provider, the payer, and the patient. As seen above in the discussion of consumers' irrational demand for brand name drugs, patients have tremendous power to influence medical decisions.²⁹⁴ Second, the public is likely to have less respect for programs that employ technocrats to second-guess physicians' prescribing decisions than for those that make use of market forces to alter prescriber behavior. Utilization management,²⁹⁵ the quintessential supply-side technique for altering prescribing decisions, has been met with significant resistance as physicians and patients view such oversight as adversarial and injurious to the doctor-patient relationship.²⁹⁶

(iii) Consumer-Driven Drug Benefits²⁹⁷

I have previously suggested, albeit in another context, that the FDA should comparatively rate drugs along three dimensions—clinical effectiveness, cost-effectiveness, and safety.²⁹⁸ Ray et al. have

²⁹³ See *supra* note 292. In actuality, New York's CSRS possesses elements of a supply-side intervention as well since physicians and hospitals likely responded to the data not only because receiving a good report card is good for business, but because they drew personal pride from being recognized as a top performer.

²⁹⁴ See *supra* Part IV.A.ii.

²⁹⁵ See Bohmer, *supra* note 290, at 15-16 (offering an excellent explanation of what utilization management entails); see generally INSTITUTE OF MEDICINE, CONTROLLING COSTS AND CHANGING PATIENT CARE?: THE ROLE OF UTILIZATION MANAGEMENT (Bradford H. Gray & Marilyn J. Field eds., 1989).

²⁹⁶ Herzlinger, *The Frayed Safety Net*, *supra* note 253, at 46.

²⁹⁷ This title, "Consumer-Driven Drug Benefits," is based on the name "Consumer-Driven Health Care," which was coined by Regina Herzlinger. See *id.* The consumer-driven model advocated here is based on several of Professor Herzlinger's writings. The reader who desires additional information about the benefits of a system that empowers patients and/or further proof that such reform will curb inappropriate prescribing (thereby reducing the incentive to design methodologically suboptimal trials) should look to the following works: REGINA E. HERZLINGER, MARKET-DRIVEN HEALTH CARE (1997); CONSUMER-DRIVEN HEALTH CARE: IMPLICATIONS FOR PROVIDERS, PAYERS, AND POLICYMAKERS (Regina E. Herzlinger ed., 2004); Regina E. Herzlinger, *Let's Put Consumers in Charge of Health Care*, HARV. BUS. REV., July 2002, at 44 [hereinafter Herzlinger, *Consumers in Charge*].

²⁹⁸ Falit, *Cheaper & Safer Drugs*, *supra* note 236, at 176-177. This article argues that a periodically updated rating system would reduce the extent to which pharmaceuti-

also argued that society would be best served by a federal body that “assesses pharmaceutical effectiveness.”²⁹⁹ Such an evaluation system, if used to eliminate methodological limitations in clinical trials, is best conceptualized as a demand-side program on the macro level but a supply-side regime on the micro level. The governmentally-sponsored rating system does not act directly on pharmaceutical companies, but rather purports to influence their behavior by altering physicians’ demand (their willingness to write prescriptions) for drugs. It thus acts to influence demand at the macro level. On the micro level, however, the system does not rely on market forces; it instead acts directly on physicians by supplying them with previously unavailable information.³⁰⁰

The establishment of a federal rating system, by itself, would do little to curb consumers’ irrational demand for heavily-advertised brand-name drugs for which there are other, more appropriate remedies. Physicians and health plans would still possess a financial interest in pleasing their customers by succumbing to their inappropriate requests. As discussed in the previous section, the ideal intervention would influence demand at both the macro and micro levels.

The American system of health care delivery has changed over the last decade insofar as consumers are playing a more active role than ever.³⁰¹ Increasing numbers of Americans see themselves as their own primary care providers who feel obligated to share in the medical decision-making process.³⁰² The time therefore seems right to grant patients the autonomy and decision-making power they desire. A comprehensive rating system, coupled with financial incentives to medicate appropriately (provided at the level of the patient), would be a demand-side intervention at both the macro and micro

cal companies distort the truth in their marketing efforts (including sales representatives’ visits to physicians), reduce drug prices without significantly impacting research and development by catalyzing an industry-wide scale back in marketing, and decrease the conflict of interest inherent in the FDA’s post-approval surveillance.

²⁹⁹ Ray et al., *supra* note 126, at 2031.

³⁰⁰ One could argue that Ray et al.’s proposal acts on the demand side at the micro level since health plans will use the information to craft better reimbursement policies and pressure doctors to prescribe drugs in a more cost conscious fashion by selectively contracting with providers who combat patients’ irrational demands. Such an argument, however, ignores the fact that under the current regime, payers—like providers—have a financial incentive to please their customers by acquiescing to inappropriate requests for brand name medication. The demand-side effect is therefore likely to be small in comparison to a system that financially rewards consumers for using pharmaceuticals in a socially rational manner.

³⁰¹ See, e.g., Herzlinger, *Consumers in Charge*, *supra* note 297; Bohmer, *supra* note 290, at 21.

³⁰² See HERZLINGER, MARKET-DRIVEN HEALTH CARE, *supra* note 297, at 47–84.

levels that could go a long way to decreasing the extent of methodological bias.

(a) Establishing a Comparative Evaluation System at the National Level³⁰³

As Ray et al. have suggested, Congress could create a federal body whose sole mission is to conduct comparative evaluations of drugs and alternative sources of therapy.³⁰⁴ The assessments would be disseminated to the public in a format that laymen can understand.³⁰⁵

The agency

would convene expert panels that would critically evaluate existing data and, when indicated, request additional data from manufacturers. This process would provide [patients with valuable information],³⁰⁶ physicians with guidelines for therapeutic decisions, and payers with the basis for managing pharmaceutical benefits, but it would not restrict the autonomy of either.³⁰⁷

As Ray et al. write, the new organization would have the power to conduct additional research if it feels that the cost of such studies is outweighed by the increased accuracy of the comparative evaluations. The system “could be funded by subscription fees from payers, contributions by payers to research on specific questions, or a very small tax on . . . pharmaceutical agents.”³⁰⁸

³⁰³ Establishing a federal rating system for pharmaceuticals is not indispensable to this Article’s proposal. The mandatory disclosure of cost and quality data (including the costs of all prescriptions) by payers and providers would likely be sufficient. See *infra* notes 329–30 and accompanying text. Such information could be compiled and translated into easily understandable, *comparative* data for laymen. Consumers could rely on these data when selecting an insurance company or provider.

³⁰⁴ Ray et al., *supra* note 126, at 2031. Alternatively, as I have previously written, the FDA could expand to take on the task of rating drugs. Falit, *Cheaper & Safer Drugs*, *supra* note 236, at 176–77. The Centers for Medicare and Medicaid Services (CMS) may be best suited to compare cost effectiveness, but if the public sector solution advocated below is adopted, CMS would cease to exist. The comparative drug evaluations are likely to become more accurate as time passes. When a drug is first marketed, it may be difficult to determine precisely how the compound stacks up against alternative therapies.

³⁰⁵ A more esoteric yet concise version could be distributed to physicians and health plans.

³⁰⁶ Ray et al. do not mention patients as potential beneficiaries of the information, which suggests that they envisioned the creation of the governmental body as a supply-side intervention at the micro level.

³⁰⁷ Ray et al., *supra* note 126, at 2031.

³⁰⁸ *Id.* Under current law, no pharmaceutical company may advertise that their compound is superior (in terms of safety or effectiveness) to another drug unless the claim has been demonstrated by “substantial evidence or substantial clinical experience.” See 21 C.F.R. § 202.1 (2007). There is no reason, however, for the federal rating body to be held to the same standard. Unlike companies advertising their own

Although Herzlinger suggests that health care quality and cost savings could be maximized by having employers provide the necessary comparative data, there are three reasons for doing it at the national level.³⁰⁹ First, employers may lack an incentive to efficiently collect and disseminate the information. If an employer is successful in reducing its workers' health care costs, improving the quality of care and catalyzing innovation amongst participating health plans, then it will likely attract a disproportionate number of sick employees. This will drive up labor costs, leaving the firm at a comparative disadvantage.³¹⁰ Second, the collective action and free-rider problems discussed above would prevent employers from reaping a full return on their investments, prompting them to invest too little in data collection.³¹¹ Health insurers are often able to keep the guidelines that sculpt reimbursement decisions hidden from the public eye since they do not release the details to their beneficiaries.³¹² Here, the purpose is to inform consumers directly so that they can make their own health care decisions, and thus, the information must be released to the patients. Without a mechanism for patenting the data, it would be impossible to prevent other companies from free-riding off of an employer's efforts. Third, employers would not be able to conduct their own studies when there are insufficient data to construct meaningful comparisons of available therapies. This is true not only because many employers lack the resources, but also because of collective action and free-rider problems. Free-riding competitors who are able to utilize the information without incurring any of the

products, the scientists creating the ratings will be impartially comparing drugs on the basis of all available evidence.

³⁰⁹ See, e.g., Herzlinger, *Consumers in Charge*, *supra* note 297. One must keep in mind that Professor Herzlinger's writings are much broader in scope than this Article insofar as they address the provision of all types of health care, rather than speaking only to pharmacological interventions. Additionally, public sector reforms seem to be beyond the scope of Professor Herzlinger's article. She assumes *arguendo* that the legal/regulatory regime which shapes the purchase the health insurance will remain fully intact. Indeed, Herzlinger has elsewhere argued that the government should establish a "health care SEC" that ensures transparency in comparative information relating to the quality of health care providers. See, e.g., Regina E. Herzlinger, *A Health Care SEC: The Truth, the Whole Truth, and Nothing but the Truth* [hereinafter Herzlinger, *Health Care SEC*], in CONSUMER-DRIVEN HEALTH CARE: IMPLICATIONS FOR PROVIDERS, PAYERS AND POLICYMAKERS 797, 797-810 (Regina Herzlinger ed., 2004); Regina E. Herzlinger & Benjamin Falit, *Long-Term Health Insurance Policies in a Value-Driven Health Care System: Implications for Physicians* (2007) (submitted for publication, on file with author).

³¹⁰ See Jacob Glazer & Thomas G. McGuire, *Private Employers Don't Need Formal Risk Adjustment*, 38 INQUIRY 260, 267 (2001).

³¹¹ See *supra* Part IV.A.iv.

³¹² Bohmer, *supra* note 290, at 19.

costs associated with producing it would be able to offer insureds comparatively low premiums.

Notwithstanding the drawbacks associated with relying on employers to inform medical consumers, Herzlinger's desire to keep government out of the business of providing comparative data is sound policy.³¹³ Such a goal, however, may be infeasible for comparative drug information. The potential need to conduct additional studies separates comparative drug data from information pertaining to the quality of health care payers and providers, as does the proprietary nature of unpublished drug data. Under any consumer-driven system (like the system I advocate here), information reigns supreme. If the solution advocated below is adopted, it is likely that private companies will emerge to compile and disseminate comparative data. Ideally, the government (i.e., the federal body discussed in this section) would stay out of the business of providing such data. The federal body's sole responsibilities would be to mandate the disclosure of information by manufacturers, and conduct additional trials that serve the public health, but for which a lack of a profit incentive makes it unlikely that industry will run them.

This ideal scenario, however, is unlikely to work in practice. In order for private-sector firms to adequately rate drugs, they must be privy to data from all published and unpublished trials, regardless of whether such studies were prematurely terminated or not. Unless legally required to do so, pharmaceutical companies are not likely to disclose the results of unpublished trials (whether the trials were completed or not) to private companies, since doing so would be akin to releasing the information into the public domain. Industry rightly views its unpublished data as proprietary information that, if leaked, would provide competitors with a competitive advantage.³¹⁴ Mandating that pharmaceutical companies disclose all data to private sector firms making comparative drug evaluations would likely be a mistake since it could significantly reduce ex ante incentives to engage in research and development. If pharmaceutical companies are able to costlessly obtain the research secrets of their competitors,

³¹³ Indeed, Regina Herzlinger and I argue in a forthcoming paper that the collection and dissemination of data pertaining to payers and providers should be performed entirely by the private sector. See Herzlinger & Falit, *supra* note 309 (discussing how governmental mandates to disclose cost and quality information for payers and providers may serve as an adequate substitute to comparative drug data).

³¹⁴ Falit, *Pharma's Commitment*, *supra* note 245, at 396 n.40 (quoting Catherine D. DeAngelis et al., *Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors*, 292 JAMA 1363, 1364 (2004); Drummond Rennie, *Trial Registration: A Great Idea Switches from Ignored to Irresistible*, 292 JAMA 1359, 1360 (2004)).

there will be an incentive to free-ride off of such information rather than expending the resources necessary to develop compounds from other sources. If a governmental organization were performing the comparative drug evaluations, however, secrecy could be more easily maintained, and industry would likely be more willing to release proprietary information to the federal body.

(b) Giving Patients a Financial Incentive to Seek Out Payers Who Selectively Reimburse Cost-effective Medicines and Providers Who Prescribe Pharmaceuticals in a Socially Rational Fashion³¹⁵

Consumer-driven health care seeks to improve the market for health insurance and health care services by creating cost-conscious, value-driven consumers who shop for health plans and medical treatment the same way that they shop for any consumer good—by examining the evidence, comparing costs, and making a decision based on personal (and often idiosyncratic) preferences. Such a system provides patients with a financial incentive to seek out health plans that selectively reimburse cost-effective medicines and physicians who prescribe drugs that offer the maximum ratio of utility to cost.³¹⁶ Consumer-driven health care boils down to the implementation of two basic principles: (1) individual purchasing and (2) wide-scale pooling of the insurance risk.³¹⁷ This section addresses each principle in turn.

³¹⁵ The ideal system would involve a great deal of change. This Article lays out the conceptual groundwork, omitting many of the nuances that would be vital to its implementation as well as a thorough discussion of the supporting literature. This is done to keep the scope of the Article manageable and allow for maximum readability. See Herzlinger & Falit, *supra* note 309 (offering a more detailed discussion of some of these concepts). Some parts of this section are adapted from Benjamin Falit, *The Bush Administration's Health Care Solution: The Proper Establishment of a Consumer-Driven Health Care Regime*, 34 J.L. MED. & ETHICS 632, 632–39 (2006).

³¹⁶ Two physiologically identical patients may need to be treated differently because one values health and/or comfort more than the other. For those patients who value comfort more than most, this may mean treating toenail fungus with an expensive product even though a generic competitor would have been negligibly inferior. In other words, society should not be concerned with convincing patients that the value they place on certain types of care is irrational. Society should, however, attempt to rid consumers of erroneous beliefs surrounding a particular drug's ability to deliver the desired type of care more effectively than alternative therapy.

³¹⁷ The creation and dissemination of unbiased, comparative information might be considered a third principle.

(1) Individual Purchasing

Inflationary pressures caused by shortages in goods and labor during World War II led President Roosevelt to create the National War Labor Board (NWLB).³¹⁸ The NWLB immediately passed the “*Little Steel* formula,” which limited employers’ ability to increase wages. Companies were therefore forced to compete for workers by expanding fringe benefits such as health insurance.³¹⁹ In an effort to “maintain the illusion that wage controls were working,” the IRS declared that health benefits are not wages and are therefore not taxable.³²⁰ The tax code followed the approach taken by the IRS during World War II; since the 1950s, it has permitted employers’ to deduct the cost of employees’ health benefits and excluded such benefits from employees’ gross income.³²¹ This double-dipping creates a system in which taxpayers fund a substantial portion of America’s health care costs.³²² The foregone governmental revenue has the same economic effect as a direct subsidy to workers who receive health benefits from their employers.³²³ The benefits of the subsidization, however, are not realized by all Americans; those who purchase health insurance in the private market (outside of employer-sponsored coverage) must pay with after-tax dollars.³²⁴

In order to unleash market forces (via the consumer) on the health care industry, one must remove the incentive to purchase health care through an intermediary (i.e., the employer). There are three basic ways in which Congress can remove the tax incentive to purchase health insurance and health care services through an em-

³¹⁸ RICHARD E. SCHUMANN, U.S. DEPT. OF LABOR: BUREAU OF LABOR STATISTICS, COMPENSATION FROM WORLD WAR II THROUGH THE GREAT SOCIETY (2003), <http://www.bls.gov/opub/cwc/cm20030124ar04p1.htm>.

³¹⁹ David B. Kendall, *A Health Insurance Tax Credit: The Key to More Coverage and Choice for Consumers*, in CONSUMER-DRIVEN HEALTH CARE: IMPLICATIONS FOR PROVIDERS, PAYERS AND POLICYMAKERS 749, 749–63 (Regina Herzlinger ed., 2004).

³²⁰ *Id.*

³²¹ I.R.C. §§ 106, 162 (2005).

³²² The employer exclusion reduces income tax revenues by over \$140 billion per year. Leonard E. Burman & Jonathan Gruber, *Tax Credits for Health Insurance*, TAX POLICY ISSUES AND OPTIONS, June 2005, at 1 http://www.urban.org/UploadedPDF/311189_IssuesOptions_11.pdf. Including payroll taxes, the total revenue loss could be as much as \$190 billion per year. *Id.*

³²³ Staff of the Joint Committee on Taxation, Excerpt from *Estimates of Federal Tax Expenditures for Fiscal Years 2005–2009*, in FEDERAL INCOME TAXATION: PRINCIPLES AND POLICIES 41, 41–46 (Michael J. Graetz & Deborah H. Schenk, eds., 2005).

³²⁴ See Burman & Gruber, *supra* note 322, at 1. There is one notable exception to this rule: if an individual itemizes deductions, then health care expenses are deductible to the extent that such expenses exceed 7.5% of the individual’s adjusted gross income (AGI) (anything above 7.5% of AGI is deductible). I.R.C. § 213 (2005).

ployer: (1) give people a choice between a tax credit (a governmental disbursement that uses the IRS's institutional competence to effectuate accurate transfers) and a tax exclusion (the right to exclude employer-sponsored health benefits from income); (2) give people a choice between a tax deduction (the right to deduct from one's income the cost of health care purchased in the private market) and a tax exclusion (the right to exclude employer-sponsored health benefits from income); and (3) eliminate the tax exemption (force employees to pay taxes on the health care benefits they receive from employers).³²⁵

(2) Risk-pooling

Risk pooling is the crux of any insurance system; at some level, the healthy must subsidize the sick. In our current regime, risk-pooling occurs at the level of the employer (with the exception of governmentally-funded insurance such as Medicare and Medicaid). If the current tax favoritism of employer-sponsored care is removed and individuals begin to opt out of employer-based risk pooling, adverse selection will run rampant. The healthiest employees will purchase experience-rated policies on the individual market, while the chronically ill are left to pool the risk amongst themselves. Without subsidization from their comparatively healthy coworkers, such individuals are likely to find employer-sponsored insurance either non-existent or prohibitively costly.³²⁶

The clearest solution to the problem is formal risk adjustment, a process whereby money is transferred according to individuals' health care needs. Risk adjustment can be performed at any one of three levels: the payer, the provider, or the patient.

Risk adjustment at the level of the patient would require distributing money (or some form of currency that can be used to purchase health insurance) to individuals in accordance with their expected health care expenditures. This can be done in two principal ways: (1) via a tax credit, or (2) via employers' disparate contributions to employees' premiums.

If implemented at the level of the payer, any given insurance company would be required to charge all individuals the same price, regardless of their health, but the government (or some body acting on behalf of the government) would level the playing field by trans-

³²⁵ The phrases "tax exclusion" and "tax exemption" are used interchangeably in this Article to refer to the fact that employees do not pay taxes on health benefits provided by their employers.

³²⁶ See Burman & Gruber, *supra* note 322, at 10.

ferring money from the insurers who enroll the healthiest patients to the insurers who enroll the chronically ill. This is essentially the model on which the Netherlands operates.³²⁷ If risk adjustment were instituted at the level of the provider, any given physician or hospital would be required to charge all individuals the same price, regardless of their health, but the government (or some other publicly accountable body) would level the playing field by transferring money from providers who deal with high-risk patients to providers who deal with low-risk patients.³²⁸

(3) One Possible Consumer-driven Regime

As long as the tax code's favoritism for employer-sponsored insurance is removed, formal risk adjustment is implemented at some level, and the government ensures that cost and quality data is readily available to the consumer,³²⁹ patients should have an incentive to seek out health plans and providers that prescribe in a socially rational fashion (taking into account the quality of post-marketing protocols). The following is merely one example of a system that has the power to curb pharmaceutical companies' use of suboptimal protocols.³³⁰

Under the new consumer-driven system, Americans would have a choice between a tax credit sufficient to purchase basic health insurance and the right to exclude employer-sponsored health benefits

³²⁷ Leida M. Lamers et al., *Risk Adjusted Premium Subsidies and Risk Sharing: Key Elements of the Competitive Sickness Fund Market in the Netherlands*, 65 HEALTH POLICY 49, 49-62 (2003).

³²⁸ While the literature dealing with the subject suggests that risk adjustment would only be needed for capitated physician groups (those that accept fees on a per-patient basis rather than a per-episode basis), this may not be the case. See Benjamin Falit, *The Bush Administration's Health Care Solution: The Proper Establishment of a Consumer-Driven Health Care Regime*, 34 J. L. MED. & ETHICS 632, 38 n.51 (2006).

³²⁹ The widespread availability of cost and quality data is a vital part of any consumer-driven regime. This section refrains from discussing this point in detail in order to keep the scope of the Article manageable. See Herzlinger & Falit, *supra* note 309.

³³⁰ This section outlines very ambitious reform with poor political viability. It offers this cursory discussion merely as an interesting example of a type of consumer-driven health care, rather than the optimal (either substantively or politically) solution. In fact, I have elsewhere suggested that the best approach may be to couple a tax deduction for individually purchased insurance with risk adjustment at the level of the payer. See Benjamin Falit, Address at the Seton Hall Law Review Health Law Symposium, *The Right Drugs at the Right Prices: Optimizing Industry-Sponsored Research by Perfecting the Healthcare Marketplace* (Feb. 16, 2007) (recording available at <http://lawmedia.shu.edu/audio/LawSymposium/LawSymposium3.wav>); see also Herzlinger & Falit, *supra* note 309 (arguing for risk adjustment at the level of the payer).

from personal income taxes.³³¹ Ideally, the tax credit would be both refundable (available to individuals who pay less in income taxes than the credit is worth) and advanceable (workers would have access to the credit at the time they have to pay insurance premiums). Individuals would be permitted to spend the tax credit on health care expenditures only.³³²

The exact amount of each credit would be based on two separate calculations. Approximately eighty percent³³³ of the credit would be equal to the cost of treating the average similarly-situated³³⁴ individual during the previous year.³³⁵ For purposes of this calculation, each patient's risk category would be based on all available evidence, including all recent medical developments. The other twenty percent of the credit would be based on an assessment, to be done at age eighteen, of the individual's expected lifetime medical requirements.³³⁶ Each year, the patient would receive twenty percent of her estimated health care costs for the year (based on her health status at age eighteen), only to be adjusted for medical inflation.³³⁷ Since this payment

³³¹ The benefits and drawbacks associated with universal health care are beyond the scope of this paper, but it is important to note that universal coverage is not necessary to the effectuation of this section's proposal.

³³² Requiring consumers to spend the disbursement on health care may encourage some overspending. Such an outcome, however, is superior to the rampant fraud that would likely result from allowing individuals to spend the credit on anything they desire. See Einer Elhauge, *Allocating Health Care Morally*, 82 CAL. L. REV. 1449, 1487–92 (1994).

³³³ The percentages used here (eighty and twenty) are open to debate. The exact percentages should be the result of extensive empirical analysis.

³³⁴ "Similarly-situated" refers to an individual's risk category.

³³⁵ Medicare's CMS-HCC risk-adjustment model could be used to determine risk categories. See generally Gregory C. Pope et al., *Risk Adjustment of Medicare Capitation Payments Using the CMS-HCC Model*, 25 HEALTH CARE FINANCING REV. 119 (2004).

³³⁶ See MEDICARE PAYMENT ADVISORY COMMISSION, REPORT TO THE CONGRESS: ISSUES IN A MODERNIZED MEDICARE PROGRAM 52 (June 2005), available at http://www.medpac.gov/publications/congressional_reports/June05_Entire_report.pdf. Given the limited short-term predictability of health care costs using the CMS-HCC risk adjustment model predictions of life-long expenditures at age eighteen are likely to be quite inaccurate. This, however, makes little difference to the model. The point is simply that some percentage of the governmental disbursement must remain constant from year to year so that consumers have an incentive to plan for the long-term. The larger the percentage of fixed disbursement, the more of an incentive there is to shop wisely and plan for the long-term, but the more likely it is that some individuals will be priced out of the market due to the onset of a costly illness. For immigrants or other individuals who become eligible for health benefits after their eighteenth birthday, the calculation would be made as soon as possible after an eligibility decision has been rendered.

³³⁷ The phrase "only to be adjusted for medical inflation" refers to the idea that, if the cost of treating someone the patient's age (not health status) went up by five per-

does not adjust along with changes in one's health status, it provides patients with an incentive to minimize health care costs over the long-term, as opposed to looking only a year ahead.³³⁸

Since consumers would be able to keep the difference between what they receive from the government and what they pay for health care,³³⁹ they would have a powerful incentive to spend wisely.³⁴⁰ In other words, the power of the purse will vastly mitigate, if not altogether eliminate, the irrational consumer demand for certain brand-name drugs, which is pervasive under the current regime. Armed with the information supplied by the newly-minted federal body empowered to comparatively evaluate alternative therapies, consumers will seek out physicians who are not improperly persuaded by methodologically suboptimal trials.

Under the current regime, employers offer their employees very few health insurance options. Instead of offering a wide array of differentiated policies, they use their purchasing power to secure two to three one-size-fits-all plans that appeal to the "average employee."³⁴¹ Forced to accept whatever plans their employer offers, employees are unable to trade off drug benefits for premiums or alternative benefits by bargaining directly with the insurance company. This inability to secure a quid pro quo creates a sense amongst employees that health care is free, and that one is entitled to the very best health care. The

cent since the individual's initial assessment, the patient would receive five percent more than the payment originally calculated for that year.

³³⁸ If 100 percent of the credit were based on the cost of treating similarly-situated individuals during the previous year, consumers would have a perverse incentive to forego therapy that would prevent them from developing serious illnesses in later years. In essence, they would have an incentive to plan only for the short term, forgoing economically efficient preventative care and lifestyle modifications. Alternatively, if one hundred percent were based on expected medical costs as of age eighteen, patients who later (after age eighteen) develop a chronic illness through no fault of their own would not possess the financial resources needed to switch to an insurer that specializes in that particular illness (or might be priced out of the market entirely).

³³⁹ Consumers could save the money for later years or spend it on more discretionary health care consumption.

³⁴⁰ Since the proposed regime would create a perverse incentive for consumers to misrepresent their health status to the government in order to receive more money, two interventions would be needed. First, the data presented to the government for risk adjustment purposes would be available to the insurance companies and providers with whom each individual attempts to contract (indeed, the insurers and providers would be providing much of the data). A person who pretends to be sicker than she really is in order to receive a higher payout would therefore have to pay an artificially high premium for insurance. Second, strict criminal penalties would be levied against individuals who intentionally or negligently defraud the system.

³⁴¹ See, e.g., Herzlinger, *Consumers in Charge*, *supra* note 297.

ubiquity of such a sentiment makes it difficult for employers to offer restrictive formularies and pharmacy benefit managers to deny claims for brand name medications. Under my proposal, consumers would be free to choose amongst a plethora of differentiated insurance options.³⁴² They would shop around for insurance companies that selectively deal with enlightened physicians, and look for innovative policies that offer lower premiums by reimbursing only the most cost effective drugs. In the individual market, prospective enrollees would be able to trade off drug benefits for other plan advantages such as lower premiums. Individuals' understanding that they are receiving something in return for accepting reduced drug benefits would allow for the creation of more restrictive formularies and make it easier for pharmacy benefit managers to deny claims in cases where their enrollees do not have a contractual right to the medication.

The elimination of employer-sponsored insurance will make it possible for payers and providers to enter into long-term contracts with consumers, thereby aligning their incentives with those of patients.³⁴³ Reciprocal long-term agreements between insurers and patients will make it profitable for health plans to reimburse interventions that are costly in the short-term but have the potential to significantly reduce long-term costs. For the first time, patient education initiatives designed to teach consumers about cost effective medications are likely to be profitable since the educating company will reap the long-term gain associated with enlightened enrollees. The use of formal risk adjustment will ensure that payers have an incentive to enroll the chronically ill and actively manage their disease with an eye toward long-term outcomes. Similarly, the lure of financial gain will lead physicians to form comprehensive care teams that focus on particular chronic diseases and secure long-term capitation contracts from insurers or the patients themselves.³⁴⁴ Such care teams will compete on cost and quality data, with the most competitive physicians demonstrating that they save payers and consumers money by, among other things, prescribing in a cost effective manner.

³⁴² Under the current regime, insurers have little incentive to differentiate themselves by specializing in particular disease processes since their primary customers are large employers with diverse employee populations. Under the proposed system, however, insurers will likely specialize to suit diverse customer needs.

³⁴³ See *supra* Part IV.A.iv (discussing how the current regime leads insurers to focus on short-term costs); Herzlinger & Falit, *supra* note 309 (discussing in detail the inherent value in long-term contracts).

³⁴⁴ Herzlinger refers to such "comprehensive care teams" as "focused factories." See REGINA E. HERZLINGER, MARKET-DRIVEN HEALTH CARE, *supra* note 297, at 157-199.

In addition to collecting and disseminating comparative data on pharmaceuticals and alternative therapies, the federal government should require the disclosure of uniform cost and quality data from payers and providers.³⁴⁵ Private sector firms could then transform this information into easily understandable, comparative data that can be disseminated to consumers. Patients who do not have the time, or simply do not care to review the federal agency's comparative drug data, can assume that a physician group is highly ranked (in part) because of its proper prescribing habits, and/or a health plan is highly ranked (in part) because it utilizes superior drug reimbursement policies and selectively contracts with providers who are not swayed by methodological limitations. Indeed, if the informational disclosure requirements are sufficiently strict, there may be no need for a federal body that rates drugs.³⁴⁶

In essence, by improving the availability of comparative data on alternative therapies and health plans, eliminating the surrogate purchasing of health insurance by employers, and implementing a program of formal risk adjustment, the market for physician prescribing decisions and prescription drug coverage will be perfected. For the first time, consumers will demand real value in their drugs and, if they don't get it, they'll take their money elsewhere. A new line of physicians will be born who remain impervious to the influence of methodologically suboptimal trials. Along with them will come a new breed of health plans that, freed from the shackles of irrational consumer demand, will design and implement innovative reimbursement policies for prescription drugs. With these two groups fighting for consumers' rights to cost effective medicine, industry sponsors will no longer have an incentive to design methodologically suboptimal studies.

V. CONCLUSION

This Article articulated several ways in which industry sponsors may have incentives to design voluntary, non-label-seeking post-approval studies that suboptimally inform the medical community

³⁴⁵ Herzlinger, *Health Care SEC*, *supra* note 309; Herzlinger & Falit, *supra* note 309.

³⁴⁶ There is no doubt that the availability of comparative data on drugs (generated by the federal body discussed above in text) would help patients to make more value-conscious choices (which in turn would curb industry sponsors' incentives to design methodologically suboptimal studies). The only question is whether consumers' increased purchasing acumen would outweigh the cost of generating the information. Given the enormous expense associated with running additional trials and producing meaningful comparative data, it is likely that society would be best served by relying on macro-level cost and quality data.

but are more likely than optimal designs to generate favorable data. It did not, however, demonstrate that pharmaceutical companies act on these incentives. Future research should attempt to determine whether industry trial designers are indeed more likely than disinterested academics to design suboptimal protocols.

Since it is likely impossible for anyone to determine, *ex post*, whether a given trial's shortened time frame, use of surrogate outcomes, or selective enrollment of subjects was socially desirable, the market may be the only mechanism powerful enough to align the interests of industry and the public health. This Article advocates the creation of a consumer-driven health care regime. Creating a health care system in which patients have the information necessary to compare the advantages and disadvantages of different treatments and a financial incentive to make value-maximizing purchases will decrease the potential profitability associated with designing suboptimal protocols. In order to attract enlightened, value-conscious consumers, payers will compete to design innovative drug reimbursement policies and providers will clamor to demonstrate that they recommend only the most cost effective therapy.