Better Regulation of Industry-Sponsored Clinical Trials Is Long Overdue

Matthew Wynia and David Boren

There is an old saw in health policy that everyone wants health care that is good, fast, and cheap — but it's impossible to have more than two of these at one time.

A similar bit of folk wisdom seems intuitively true for the development and testing of new pharmaceutical products. The public is in a bind. We want breakthrough drugs, and fast. But we also want these drugs to be affordable, thoroughly tested, safe, and effective. It seems we can't have it all.

In this paper, we will not claim that one can have it all — but that we can do far better than we are at present. First, we review extensive data on contemporary problems in the design, conduct, and analysis of industry-sponsored clinical trials. Finding major issues that have been solidly documented over more than a decade, we provide many examples of the multifarious ways in which industry-funded trials have been manipulated to raise the likelihood of producing industry-friendly results. Having explored these issues in some detail, we will then argue that the number and variety of ways in which industry funding can affect research are so great and so difficult to detect that it will not be possible to manage these conflicts effectively without building a professional firewall between industry funding and the design, conduct, and reporting of late-phase clinical trials.

Background

Regulating the development of new drugs is fraught with risk.[1] Misguided regulations can slow drug development, raise costs, and hurt desperate patients in need of new medicines. For one of us (MKW), an AIDS specialist, it is hard to overstate the risks of slowing the process for testing new drugs. People can and do die while awaiting drugs that are slowly winding their way through the development and testing pipeline. On the other hand, some regulatory choices that might increase the speed of release of new drugs might also allow drugs on the market that are later deemed unsafe. Under current regulations, about 20% of newly approved drugs are eventually pulled from the market or have major safety warnings ("black box warnings") attached to them.[2] A recent doubling of reported severe adverse drug effects might also stem from ineffective drug testing processes.[3] In addition, ineffective regulation can push short-term market forces, rather than medical needs or scientific advancement, to drive

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drug development. Moreover, completely unregulated drug development could actually stifle true innovation, since a completely unregulated market would foster trade secrets, to prevent knock-offs and other property-rights infringements.

We also acknowledge that some criticisms of the drug industry are overly simplistic. For instance, not all problems lie with the fact that pharmaceutical firms are motivated by profit. The profit motive is complex, and it can be harnessed for the good of society. After all, the long-term success of companies lies in developing new products that are ultimately proven safe and effective, maintaining the trust of the public, and living up to a clear mission that all company employees, and the public too, can believe in.[4]

At the same time, economic drivers can contribute to the problems we see. For instance, it might take a billion dollars and ten years or more to bring a drug through testing to market — by that time, the patent life might be too short, the legitimate market for the drug too small, or the competition too quick to bring out rival drugs, making it hard to recoup the investment and driving intense efforts to create rapid, blockbuster sales. Recently, we saw an example of the problems such pressure can cause when Merck's breakthrough vaccine for Human Papillomavirus, Gardasil®, approved in June 2006, was threatened with the imminent arrival of GlaxoSmithKline's competing vaccine, Cervarix®. The push to boost early sales led Merck, inappropriately, to pressure legislators to mandate use of Gardasil, eventually prompting a backlash within the public health community and creating another blemish on Merck's public image.[5]

Finally, we should acknowledge the tendency to personify pharmaceutical companies, and the related tendency to think of them as we might individuals when considering regulatory choices. The pharmaceutical industry is not a moral entity and corporations are not people. Of course, industries and the companies within them are reflections, in part, of the people who run them. More importantly, however, companies reflect the regulatory structures that we, as a society, choose for them, and these regulatory structures can make it easier or harder for the people running companies to act in accordance with their moral duties. In other words, unlike people, corporations are created ("incorporated") by virtue of our social choices about regulatory structures. One result is that, though it is rhetorically appealing to some, it is not possible for the drug industry to be governed only by the so-called "free market." Legal rules govern the very existence of corporations, and our regulatory choices define the "industry."

Since industries are not "natural" but are created by our regulatory choices, our overarching question is not whether or how much to regulate — even a choice not to regulate is a positive social choice about the regulatory structures that define the industry — but rather, what sorts of regulatory structures for new drug testing will provide the greatest likelihood of optimal social benefits?

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In this regard, optimal regulatory structures should ensure a level playing field and make it easier for pharmaceutical industry leaders to act in the public interest, as most would like to do. One industry analyst, speaking about calls to reduce marketing expenditures and increase research funding, said, "I don't know a single CEO who wouldn't prefer to trade salespeople for research. [But] you can't unilaterally disarm."[6] Carefully implemented uniform regulations can make doing the right thing much easier for the people struggling with moral choices within the pharmaceutical industry.

With these issues addressed, let us move on to the main questions for this essay.

Do Industry-Funded Trials Produce Industry-Friendly Results?

A series of articles over more than a decade have consistently demonstrated that industry-funded trials tend to produce results that favor the company sponsoring the trial. Recently, for example, Paul Ridker and Jose Torres reviewed 205 studies (published in 2000-2005) of new drugs for cardiovascular disease in top-tier journals.[7] Of those funded by not-for-profit organizations, 39.5% came out in support of the new drug; among those funded by industry, 65.5% supported the new drug. Bodil/Als-Nielsen et al. reviewed 370 studies and found that the odds ratio (OR) for industry-funded studies to provide industry-friendly results was 5.3 (CI 2.0-14.4).[8] Lisa Bero et al. in a multivariate analysis of 192 studies of statin drugs, 95 of which were funded by industry, found that industry funding was "the main factor" leading to both positive results and stronger conclusions.[9] They conclude that

industry-funded randomized controlled trials (RCTs) "of head-to-head comparisons of statins with other drugs are more likely to report results and conclusions favoring the sponsor's product compared to the comparator drug."[10]

In fact, there have been so many such studies that several recent studies have been meta-analyses. Joel Lexchin et al. reviewed 30 different studies looking at the relationship between industry funding and trial outcome or reporting: the overall odds of industry-funded studies reporting industry-friendly outcomes was 4.05 compared to non-industry-funded studies (95% confidence interval [CI] 2.98-5.51).[11] Justin Bekelmen et al. examined 8 prior reviews, which combined the results from 1,140 original studies, and showed a pooled OR of 3.60 (CI 2.63-4.91) that industry funding leads to industry-friendly results.[12] In these and other studies, industry sponsorship seems to be associated with at least a 3-to-5-fold increase in the odds that the trial will come up with results, and/or the authors will come to conclusions, that favor the new product.

Given the consistency and strength of these findings, then, we must ask: Why?

Is industry-funded research of poor quality? This has been studied several times, and, at first blush, it does not appear to be true.[13] Granted, in some studies of quality, the researchers excluded poor quality reports from their reviews (e.g., Als-Neilson et al. looked only at studies in the Cochrane database, which excludes poor quality studies[14]). But industry researchers also understand the ways quality is measured, and it is not very difficult, given enough resources, to meet typical quality standards. For example, most studies use the Jadad score to measure trial quality, but the Jadad score considers only randomization, blinding, and the number of study dropouts.[15] As we shall see, there are many, many other ways to produce research that is likely to favor a new product.

Another possible explanation is that industry-funded researchers do high quality research but publish only favorable results. In fact, negative results have been suppressed[16] and positive results published in multiple venues or in multiple different reports,[17] exaggerating the apparent importance of the latter. Such selective publication is unethical. The resulting bias in the literature can affect subsequent reviews and meta-analyses, and problems arise when doctors and patients make treatment decisions based on skewed or partial data. Misleading suppression of negative and republication of positive data has led to increasing calls for public reporting of all clinical trials at the time they are initiated,[18] as well as demands by researchers that they be allowed to publish clinical trial results regardless the outcome.[19] One might also argue that more thorough peer review could pick up on duplicate publications, though such reliance on volunteer peer reviewers might be misplaced.

A third possible explanation is that industry-funded investigators are not truly in "equipoise" when they start a clinical trial.[20] That is, industry sponsors might carefully select medications to test so that most of them will be successful. Strictly speaking, this could also be an ethical breach — many experts in the ethics of human subjects research believe that researchers should not already believe that one treatment is superior to the other when starting a trial — but it might also mean that drug developers are doing a very good job of producing drugs that are likely to be effective, because they are designed well, tested well in animals, and based on reasonable physiologic mechanisms of action. As a result, by the time they reach late-stage clinical trials, these new drugs might be expected to produce mostly positive results.

Finally, the most concerning explanation, and most relevant for this paper, is that industry-funded clinical trials might be improperly designed, conducted, and analyzed such that they favor industry products. If this is happening, then significant changes to the regulatory structure might be needed, above and beyond a clinical trials registry and professional insistence on the right to publish research results.

We will briefly examine evidence regarding inappropriate industry influence on the design, conduct, and analysis of trials in turn.

Inappropriate Clinical Trial Design

There are a number of ways that an industry sponsor might influence clinical trial design to increase the possibility of producing industry-friendly results.[21] Many of these result in trials that do not provide optimally useful clinical data that can, or should, inform care. Importantly, many are also hard to detect during peer review, and none would appear in a typical assessment of trial quality using the Jadad criteria. The following is a partial list, with examples of industry-funded trials that have used each technique.

Use an Inappropriate Comparison Drug

There are a number of examples of industry sponsors testing a new drug against an old drug that is known to be ineffective. According to Helle Johansen and Peter Gøtzsche, in three published trials "comparing a new antifungal agent, fluconazole, with amphotericin B in patients with cancer complicated by neutropenia…results for amphotericin B were combined with results for nystatin in a 'polyene' group. Because nystatin is recognized as an ineffective drug in these

circumstances, this approach creates a bias in favor of fluconazole."[22] These three trials made up 43% of the patients in meta-analyses comparing fluconazole with amphotericin B in patients with neutropenia, which "compromised the results of the meta-analysis." In other instances, Johansen and Gøtzsche found that "patients were randomized to receive oral amphotericin B, which is poorly absorbed and not an established treatment."[23] In cardiovascular medicine, Bruce Psaty et al. noted the use of Atenolol as a comparator drug in several recent large hypertension trials, despite the fact that Atenolol is not effective in preventing cardiac mortality in this setting.[24]

Use an Inappropriate Dose of the Comparison Drug

This strategy has been used both to boost the apparent efficacy of the new drug and to reduce the chance of detecting toxicity. For instance, Daniel Safer found "at least eight studies sponsored by three different drug companies [that] compared their second-generation neuroleptic drug to a fixed high dose of haloperidol of 20 mg per day…(This) ensures that the second-generation product will have fewer extrapyramidal side effects than haloperidol."[25] Moreover, according to Safer, "doses of haloperidol exceeding the customary levels of 4 to 10 mg/day produce no better clinical results than do doses above that range," helping to ensure the new drug would also not be found less effective. In another example, Lisa Bero et al. reviewed "42 RCTs comparing the low-density lipoprotein–lowering ability of two or mores statins," and found that "almost all of the trials compared non-equivalent doses of statins."[26]

Howard Brody recounts an especially striking story about the use of this strategy.[27] When Schering Plough was preparing to bring loratidine (Claritin®) to the U.S. market, they submitted data to the FDA on a 10mg dose, which proved to be about 10% better than placebo at relieving allergy symptoms. Although that is not very effective, more important for Schering's plans was that loratidine is not sedating at this dose. At higher doses it is more effective, but it also becomes more sedating. Schering didn't raise this with the FDA, however, because, according to Brody, they wanted to market the drug as a "non-sedating" antihistamine. And indeed, once it was approved, it became a blockbuster. Many patients eventually discovered they had to take a higher dose — and tolerate the attendant sedating effects — to get relief, but by this time the marketing plan had worked. Schering was selling 2 billion dollars of Claritin per year.

Another example of selecting an inappropriate comparison dose is the case of AstraZeneca's older drug omeprazole (Prilosec®), which has been "directly" compared to AstraZeneca's newer drug esomeprazole (Nexium®) for relief of gastric reflux symptoms and other indications. These studies, however, often fail to account for the fact that esomeprazole is merely the active L-isomer of omeprazole — that is, they are *the same drug*, but one contains double the amount of active ingredient per gram. This makes it relatively easy to prove the latter is superior when both are taken at the "same" dose. Such results can then be used to declare that "Esomeprazole provides improved acid control vs omeprazole."[28] Not coincidentally, "discovering" the L-isomer of an existing drug is also an effective way to extend patent protection.

Compare the New Drug to a Placebo

To provide a new medicine with the best possible chance of being proven effective, and as quickly as possible, one can compare it against a placebo. Such trials can be justified but are often less informative than head-to-head trials, since placebo is rarely the best available treatment. Nevertheless, Benjamin Djulbegovic et al.'s meta-analysis of randomized trials for multiple myeloma found that industry-funded trials were about 3 times as likely to pit new drugs against placebo, and new drugs were "strongly favored when the standard comparative treatment was placebo or no therapy."[29]

Underpower the Study

In research lingo, underpowering a study tends to increase "type II" errors. Type II errors arise when a study fails to detect a difference that actually exists. Studies can be statistically underpowered in several ways. For instance, Psaty found multiple instances of very short-term trials of new anti-hypertensives, which reduces the chance of detecting long term adverse events or of showing the new drug to be ineffective at preventing long-term cardiovascular complications.[30] James Brophy suggested that the manufacturer of Muraglitazar (a diabetes treatment) underpowered a major study, ensuring that it would fail to detect "meaningful safety differences."[31]

Another reason to underpower a study would be to avoid finding any differences, good or bad, between a new drug and an old drug. Why would a manufacturer want to conduct a study only to show that its new drug is no better than an old drug? Because often that's all that is required to get the new drug on the market.[32] The rationales for these so-called "non-inferiority trials" are complex, and sometimes valid, but the use of this very low bar has been questioned, especially in cases where existing therapies are of minimal efficacy compared to placebo.[33]

Use Exclusion and Inclusion Criteria to Select the Study Population for Optimal Results

In a 2005 meta-analysis of published phase III trials of etanercept (a new drug for rheumatoid arthritis), Pendar Farahani et al. found many discrepancies between how the drug was used in trials and how it was to be used in actual clinical practice.[34] In short, they found that phase III clinical trials had been conducted in idealized conditions with strict exclusion criteria, some of which seemed designed to ensure that only those patients most likely to benefit from the new drug would be enrolled. Similarly, one criticism of the data on the diabetes drug muraglitazar presented to the FDA was that elderly patients were excluded, even though more than 1/3 of type II diabetics are elderly.[35] And Saul Malazowski notes that a prominent RCT of exenatide combination therapy for diabetes (which was also "much too small and much too short" and hence provided "a false sense of safety") failed to ensure that enrolled patients were on optimal therapy prior to beginning the trial.[36] This raised the likelihood that "metabolic control would be suboptimal" among enrollees, which would "enhance the [apparent] effect of any [new] medication."

Don't Report Undesirable Endpoints

If a new drug is anticipated to have an adverse effect on certain outcomes, the sponsor might design a trial that does not follow those endpoints. For example, congestive heart failure (CHF) has been excluded from composite "heart disease" measures in trials of antihypertensives that are known to exacerbate CHF.[37] A related strategy is to stop collecting data on adverse events early in the study. For example, the VIGOR study of rofecoxib (Vioxx®) in rheumatoid arthritis followed cardiac events, which were suspected to be higher in Vioxx users, but did not report on cardiac events that occurred in the last part of the trial, hence excluding several late heart attacks from their analysis.[38] Similarly, the investigators in the CLASS study of Celebrex for arthritis pain presented only 6 months worth of data on gastrointestinal toxicity, purporting to show a reduced risk of bleeding, though 12 months of data were available and showed no overall reduction in bleeding.[39]

Use Surrogate Markers Rather Than Clinical Endpoints

Surrogate markers are laboratory or clinical findings that do not represent the final hoped-for endpoint of medical therapy, though they are thought to be correlated with the desired outcome. As with using placebos and non-inferiority trials, the rationales for using surrogate endpoints are complex and often reasonable. For instance, HIV treatment trials often follow CD4 cell counts and measures of the HIV viral load, rather than tracking deaths or illnesses. These surrogate markers have been tightly linked to disease outcome, so using them makes sense — but it is not without risk. While following surrogate markers can speed up clinical trials and provide results with many fewer trial participants, they can also lead to mistaken conclusions about final endpoints. There are many instances where the link between the surrogate marker and the final clinical endpoint of interest has turned out to be tenuous, or even contrary to what was expected. Fluoride raises bone density, but it doesn't work for osteoporosis because it makes bones brittle and even more likely to fracture.[40] Estrogen raises HDL (which has been associated with lower risk of heart disease), but post-menopausal estrogen supplementation actually increases the risk of heart disease.[41] Some drugs that reduced episodes of heart arrhythmias unexpectedly led to more cardiac deaths.[42] And recent studies have shown that some drugs that reduce hemoglobin A1c (a marker of blood sugar control) in diabetics might nevertheless increase their risk of diabetic complications such as heart disease.[43]

Some studies, such as "seeding trials," are not intended to answer a research question at all, but only to create marketing data or to raise practitioners' awareness and use of a new drug. It is not clear how common such trials are — they are sometimes called "formulary acceptance" or "provider experience" trials — but some have been criticized as little more than kickback schemes for prescribing physicians, who are paid to "enroll" patients.

Conduct Scientifically Irrelevant "Seeding Trials"
Some studies, such as "seeding trials," are not intended to answer a research question at all, but only to create marketing data or to raise practitioners' awareness and use of a new drug.[44] It is not clear how common such trials are — they are sometimes called "formulary acceptance" or "provider experience" trials — but some have been criticized as little more than kickback schemes for prescribing physicians, who are paid to "enroll" patients.[45] "Seeding trials" are marked by "the use of a design that does not support the stated research goals…recruitment of investigators not because they are experts or leading researchers but because they are frequent prescribers of competing products in the same therapeutic class…disproportionately high payments given to investigators for their work…sponsorship of the studies by the company's sales and marketing division rather than its research department… minimal requirements for data…[and] the collection of data that are of little or no value to the company."[46] Patients are presumably never informed of the true (i.e., marketing) intent of these "trials."

Inappropriate Conduct of Clinical Trials

Even if a clinical trial is well designed to address a relevant clinical question, it is possible for the researchers involved to conduct the trial poorly. Of course, any study can be conducted poorly — scientific misconduct and fraud occur in both industry-funded and nonprofit-funded research — but some factors underlying misconduct in industry-sponsored research are related to its inherent incentives: namely, the powerful incentive to produce positive results quickly. Timothy Caulfield cites industry documents claiming "drug companies stand to lose between $600,000 and $8 million each day clinical trials delay a drug's development and launch."[47] Brody relates a similar estimate, that every day of delay in approval costs the sponsoring company $1.3 million.[48] Whatever the exact number, rapid results are tremendously valuable to the sponsor.

Provide Extreme Incentives to Enroll Patients
To speed up enrollment, industry sponsors often provide physicians with especially large financial and nonfinancial incentives. Payments per enrollee can reach into the thousands of dollars. Among industry sponsors, Janssen has paid physicians $3,600 per patient for a migraine drug trial; Organon Inc paid $1,100 per patient for a study of birth control pills; Wyeth-Ayerst paid $4,581 per patient for testing hormone replacement drug; and Ibah Inc. (a drug testing company) provided $750 or $500 bonuses to physicians for each patient who enrolled in a trial before certain dates.[49] In other cases, strong non-financial benefits, such as authorship on journal articles, have been alleged to rest on meeting enrollment targets.[50]

If one assumes such incentives are effective (economists would not question this; nor would study sponsors, who must believe incentives work or they would not offer them) and assumes that a practice will have a limited number of qualified potential enrollees, increasingly strong incentives will predictably increase the incidence of physicians enrolling unqualified patients in these trials. Indeed, facing these incentives some physicians have resorted to "massaging entry criteria"[51] to enroll more patients, while others have engaged in outright fraud, enrolling patients who did not even have the disease under study.[52]

Work with Unqualified Researchers
In an effort to enroll patients as quickly as possible (and possibly to avoid scrutiny by experienced researchers), industry has increasingly turned away from working with academic medical centers, in favor of working through Contract Research Organizations that, in turn, work with physicians in private practice. Many of these new physician-investigators have very little experience in the conduct of clinical trials, which raises the possibility of misconduct, either by accident or intent.[53] In some cases, physicians have agreed to practice beyond their domain of expertise in order to participate in lucrative clinical trials. In some trials, "Psychiatrists have conducted pap smears and asthma specialists have dispensed experimental psychiatric drugs."[54] In other cases, physicians with serious practice-related problems have nevertheless been allowed to recruit patients into clinical trials.[55]

Inappropriate Analysis and Reporting of Trial Results

Finally, even with a well-designed, well-conducted clinical trial, it is possible to meddle inappropriately in the analysis and reporting of the results. Indeed, Als-Nielsen et al., in a review of 370 RCTs, found that, after careful adjustment for many other variables, "Conclusions in trials funded by for-profit organizations may be more positive due to biased interpretation of trial results."[56] This remained true even after adjusting for the magnitude of the treatment effect and the occurrence of adverse events during the trials. In other words, regardless of the outcome, industry-funded studies were more likely to be interpreted positively by the investigators.

Study sponsors often control access to the data,[57] and as noted earlier, selective publication has been a problem. For example, Brody reports that the manufacturer of paroxetine (Paxil) conducted 5 studies of the drug in depressed children, only one of which

showed benefit, and several of which showed potential harms. Only the single trial showing benefit was published, and it was heavily promoted.[58] This does not appear to be an isolated instance, since in a review of 42 studies used to support approval of anti-depressants in Sweden, Hans Melander et al. found multiple instances of both selective and duplicate publication of positive data in industry-funded trials.[59]

Data interpretation can also be affected by how the data are reported. For instance, K.S. Knox et al. found that industry-funded studies were less likely than non-profit-funded studies to report relevant interpretive information, such as whether it was reasonable to extrapolate the findings to other clinical settings.[60]

Another inappropriate analysis strategy is, to paraphrase Brody, to shoot first then paint the target around where one's arrow lands. In other words, following study completion, one can search through the data looking for positive findings to emphasize in publications. This is called "data dredging," which is highly susceptible to finding false positive results, but it is very difficult to discover this sort of manipulation if one does not have information about the original study design. Retrospective descriptions can easily make it sound like the study intended to track the reported measure all along. Imagine, for example, that one is testing a new drug to prevent heart attacks. The initial look at the data shows that it has no effect on cardiac deaths overall, but it does reduce the incidence of a certain sub-type of heart attacks. The report on the drug can then focus on just that certain subtype of heart attack. In fact, sulfinpyrazone was nearly brought through the FDA-approval process in just this way.[61]

Investigators who insist on publishing industry-funded research that does not reflect well on the new product have sometimes faced harsh penalties. One must acknowledge that it would require a stiff sense of professional duty to stand up to one's funder and insist on publication of results the funder wants to hold back. The cases of Nancy Olivieri and David Healy have become bywords for the potential consequences of bucking the desire of industry to avoid the release of negative findings.[62] Both of these cases are complex, but the bottom line is that both researchers faced serious financial and career pressures as a consequence of openly discussing their interpretations of their research.

Ghost Authorship

Skewed industry-written results can be made more credible if they are presented as the work of respected academics. This is referred to as the problem of "ghost authorship," because the real author is invisible — hidden behind a purported author who essentially just lends his or her name to the project.[63] The problem seems to have been around virtually since the advent of the pharmaceutical industry itself,[64] and it shows little evidence of fading despite it being clearly unethical on the part of the purported author who accepts the work of others as his or her own.[65] In one recent instance, the purported first author of a major report on Vioxx, which had been manipulated to reduce the number of apparent cardiac deaths, was confronted with discrepancies in the paper. He replied that he had never seen the raw data on which the trial was based and that "Merck came to me after the study was completed…[and] the initial paper was written at Merck, and then it was sent to me for editing."[66]

There is very strong evidence that industry-funded trials tend to produce industry-friendly results. These results often reflect poor science and information that is not helpful, and maybe harmful, to clinicians and patients.

What Should Be Done?

In sum, there is very strong evidence that industry-funded trials tend to produce industry-friendly results. These results often reflect poor science and information that is not helpful, and can be harmful, to clinicians and patients.

This situation is, or should be, intolerable to patients, clinicians, and the pharmaceutical industry too. After all, trust in the pharmaceutical industry is critical,[67] and recent surveys show it to be in jeopardy.[68] Good information is needed for anyone who becomes a patient — which is to say, virtually everyone. And clinical trials are expensive, and research volunteers are not an unlimited resource. It is imperative that we design and carry out the best possible clinical trials with the resources we have.

While all these points are clear, how to improve the situation remains a fraught question. Considering the myriad ways in which industry sponsors of research can manipulate clinical trial design, conduct, analysis, and reporting, a simple fix is unlikely to address all

the potential weak spots. Moreover, any change in the regulatory structure will entail costs and risks as well as potential benefits.

Recent changes, which were clearly needed, include the strong movement towards a clinical trials registry and an insistence that researchers maintain access to clinical trials data and the right to publish trial results without interference by the funder.[69] Top-tier medical journals now demand that clinical trials be registered.[70] Many now expect authors to disclose whether they controlled decisions about how to analyze and report the data.

Many other ideas to improve the regulatory structure have merit. For instance, to reduce the financial incentive to rush clinical trials, the patent clock should start counting down at the time of drug approval rather than the time of registration. To make it easier to detect post-hoc, selective analyses, journal peer-reviewers should be given standard information about the original designs of clinical trials (such as pre-determined endpoints).[71] There should be better training of all clinicians involved in recruiting for clinical trials, including on the ethics of informed consent and the rights of patients in trials. And there should be a standard and secure way for clinicians involved in trials to report problems, as anonymous whistle-blowers if necessary.

Note that these and other structural and procedural changes, taken together, do not necessarily constitute an increase in regulation — nor are they clearly a decrease; they would, however, change the regulatory environment.

Yet even if all of the above changes were put in place, they could not mitigate all the various ways in which trials can be manipulated to raise the likelihood of producing the results the funder wants. Nor can they ensure that investigators — who are, after all, human — would insist on reporting negative results in the face of a clear desire not to do so on the part of their direct funders.

Given the need for investigators to get along with their funders, and the fact that industry funds most clinical trials today, it should be no surprise that we can easily find so many examples of trials that have been manipulated to favor the sponsor. The options for mischief are many, incentives to use them strong, and opportunities abundant.

Therefore, if we are serious about creating an effective clinical trials system — one that fully respects the human subjects involved, with clinical trials carefully designed to produce useful information, and where both negative and positive results are reported honestly — there must be a change in the fundamental structure of the relationship among industry, investigators, and regulators. In short, there should be a professional firewall established between industry financing and final decisions about trial design, conduct, analysis, and reporting. In other words, late-stage industry-funded trials should pass through an independent system of professional review, which can ensure that research questions are carefully formulated, study designs are well planned and implemented, and analysis and reporting are as complete and unbiased as possible. This professional review process should include both public and private sector stakeholders, but the key is that it should be transparent and driven by medical science, not marketing demands.

This may sound utopian (what about intellectual property protections, and who would fund such a structure, one might ask), but in fact there are examples where something like this seemingly revolutionary structure is already in place and relatively well functioning. In AIDS care, for example, the AIDS Clinical Trials Group (www.aactg.org) is a partnership that is funded by the NIH, but that does useful clinical research using novel private sector drugs. Its work is extremely well respected, albeit slower and more complex than some would prefer, because each of its clinical trials is carefully vetted through an expert review process to ensure that the research questions are clinically relevant and the study is designed to actually answer the questions. Similar organizations exist in oncology, where the clinical stakes are high and patient advocacy groups are active. Notably, in both of these areas head-to-head trials have become common and placebo-controlled studies are rare. Moreover, in part because of the relatively high scientific quality of the work in these groups, new drugs in AIDS and cancer are often approved in record time, and there have been few scandals where shoddy research in AIDS or cancer has led to an inappropriate drug approval.

Based on these types of experiences, industry leaders might understand that an effective public-private partnership to coordinate and oversee clinical trials could well facilitate, rather than slow down, FDA review of new drugs. For instance, central or regional IRB review could reduce the time from trial design to implementation.[72] The FDA should be involved in this review process, so that all stakeholders would have a better sense of whether a proposed protocol could lead to approval, thus reducing the number of products that have to be turned back for more study.

Additional details of such a restructured process for ensuring that clinical trials are well designed, conducted, and analyzed are well beyond the scope of this essay, but others have suggested more detailed plans.[73] One point regarding funding is important, however.

Funding should come from both the government (probably through the NIH) and private industry, but the total cost of such an endeavor should actually be much less than current expenditures, while producing better, more useful results. Although it is true that good studies can cost more to conduct than poor quality studies, the value of poor-quality studies is low or even negative. Today we see far too many studies that do not add scientific value. In addition, promoting useful studies might create additional savings if it leads to more effective use of medicines, more appropriate dosing, and so on. In this regard, a public-private clinical research review function could be attached to a comparative effectiveness research enterprise, which is an idea with increasing political currency.[74]

Conclusion

There are innumerable ways in which an industry sponsor can manipulate a clinical trial to make it more likely that the results will favor the sponsor's product. Some reforms of the regulatory process are underway, which might curtail certain egregious practices. But the fundamental structure of industry-sponsored research today is that industry directly finances, and thereby controls, the design, conduct, and reporting of research on its own products. This produces tremendous financial incentives to design, conduct, and report scientifically questionable studies. Not surprisingly, these incentives work; and as they lead to scandal after scandal, they have led to patient harms as well as pervasive mistrust of the pharmaceutical industry, industry-funded research, and medical scientists working with industry. If we hope to restore trust and promote high-quality, medically relevant clinical trials, these basic incentives will need to be mitigated by putting a professional firewall between industry funding and final decisions about clinical trial design, conduct, analysis, and reporting.

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