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PHARMACEUTICAL-INDUSTRY SPONSORED RESEARCH: PROMOTING TRANSPARENCY

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Abstract

Strong, evidence-based practice requires that objective, unbiased research is available to inform individual clinical decisions, systematic reviews, meta-analyses, and expert guideline recommendations. Seeding trials, publication planning, messaging, and ghostwriting, as well as selective publication and reporting of trial outcomes have been used by industry to distort the medical literature and undermine clinical trial research, explicitly by obscuring information that is relevant to patients and physicians. Policies that promote transparency into the clinical trial research process, through improved and expanded disclosure of investigator contributions and funding, comprehensive publicly-available trial registration, and independent analysis of clinical trial data, have the potential to address these subversive practices by improving accountability among industry and investigators. Minimizing the impact of marketing on clinical trial research,

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and strengthening the science, will protect both the integrity of the medical literature as well as the public's health.

Evidence-based medical practice requires that objective, unbiased research is readily available to clinicians, investigators, and regulators, which can be used to inform individual clinical decisions and for systematic reviews, meta-analyses, and expert guideline recommendations. However, there is increasing awareness and concern about the role of industry in clinical research and its impact on the medical literature, partially driven by research demonstrating a positive relationship between sponsorship and findings. For instance, a meta-analysis of 1140 original research studies found that industry-sponsored trials had 3.5 times greater odds of reporting pro-industry conclusions.[1] Subsequent meta-analyses confirmed this finding among both medical and surgical[2] and recent major cardiovascular randomized controlled trials.[3]

Collaborations between academic physicians and industry are essential to advancing scientific knowledge and improving the care of patients. However, there have been a number of recent exposés describing problems with industry-sponsored trials, including issues related to withholding of trial data, involvement of marketing, inappropriate authorship, and lack of accountability. These and related concerns remain a dominant issue in public and professional discourse.[4–8] In this commentary, we review several practices that have been used by industry to distort the medical literature and undermine clinical trial research, explicitly by obscuring information that is relevant to patients and physicians. We subsequently describe the value of promoting transparency to address these practices, specifically describing the need for improved disclosure and registration practices and independent analysis of clinical trial data.

DISTORTION OF THE MEDICAL LITERATURE

A wide variety of research practices have been previously described as being used to distort the medical literature in favor of a clinical trial sponsor's pharmaceutical intervention,[9–13] although many are less common due to the larger role institutional review boards (IRBs) and information technology now play in clinical trial research. For instance, comparing a drug to a less effective active control was described among trials of antifungals for infected cancer patients with neutropenia[14] and of various anti-hypertensives.[15] Similarly, comparing a drug to a high-dose active control, at a dose high enough likely to lead to greater adverse side effects, was described among trials of selective serotonin reuptake inhibitors for depression and anti-psychotics for schizophrenia.[16] However, IRBs make these practices less common today. As another example, "salami slicing,"[17] publishing separate, but similar, articles that rely on the same set of data, has been described among trials of nonsteroidal anti-inflammatory drugs (NSAIDs) for rheumatoid arthritis,[18] of risperdone for psychosis,[19] and most recently, of duloxetine for depression.[17] However, the increased use of the internet and PubMed, the on-line MEDLINE search engine managed by the National Library of Medicine (NLM), makes this practice less common as well.

Nevertheless, several related practices remain common and three deserve further discussion: (1) seeding trials; (2) publication planning; and (3) selective publication and reporting (Table 1). Each undermines the clinical trial research process through acts of commission or omission, obscuring information from physicians and the public and distorting the medical literature. We will describe each practice, using illustrative examples, and then discuss the potential for greater transparency to address each.

Seeding Trials

Clinical trials designed by industry to promote the use of pharmacotherapies are known as marketing or seeding trials.[20–24] Although they are deceptively designed to appear to be answering a scientific question, seeding trials primarily pursue marketing objectives, promoting a medication or device and encouraging its use directly to prescribers under the guise of their participating as an investigator in a clinical trial. Seeding trials tend to study medications that were recently approved or are currently under review by the Food and Drug Administration (FDA), influencing prescribers as the company puts their product in the hands of practicing physicians, hoping that the experience treating patients with the study drug and a pleasant, even profitable, interaction with the company will result in more loyal physicians who prescribe the drug.[21]

Seeding trials undermine the clinical trial research process in several ways. First, the true objective of the trial, to market and promote a new drug to physicians, is not disclosed to patients, physicians, or IRB members. This non-disclosure prevents patients from making fully informed consent decisions about participation, but also affects the physician investigators, who are the actual study subjects as companies systematically examine the impact of participating as a trial investigator on subsequent prescribing.[24, 25] Second, these trials may be less likely to be published, since they are designed and conducted by marketing, a problem we will discuss below. Finally, these trials are often redundant and examine scientific questions that have already been formally investigated by the company.

As an example, we reviewed documents produced as a part of litigation against Merck related to rofecoxib, a cyclo-oxygenase-2 inhibitor used to treat osteoarthritis, finding clear evidence that Merck had conducted a seeding trial to promote the prescription of Vioxx by physicians that coincided with the FDA's approval and the availability of the product on the market.[25] The objectives of this trial,[26] as described by marketing executives, were "to provide product trial among a key physician group to accelerate uptake of VIOXX as the second entrant in a highly competitive new class … and was designed and executed in the spirit of the Merck marketing principles".[25] Further clarifying the true purpose of the trial, executives summarized by saying:

> "Finally, the results of the trial are being carefully tracked. An analysis at 6 months post [market availability] demonstrated significantly higher level of prescribing for VIOXX among primary care [trial] investigators compared to a control group of prescribers. Feedback from the field [pharmaceutical representatives] has been overwhelmingly positive about the ability to access key customers and the influence that being involved in the trial has had on [prescribers'] perception of VIOXX and Merck."[25]

Two other litigation document reviews, in this case examining documents produced as part of litigation against Pfizer and Parke-Davis, Division of Warner-Lambert Company, related to gabapentin, an anti-epileptic medication that is also commonly used to treat neuropathic pain, similarly showed that a large clinical trial was used for marketing by encouraging "key customers" (i.e., neurologists) to participate in research, to advance promotional themes, and to build market share.[24, 27]

Publication Planning

Publication planning involves the organizational and practical work of shaping industry trial data and turning it into medical journal articles, a practice that goes beyond routine plans for dissemination of science because plans are designed to explicitly create and communicate information to support productmarketing.[28–31] The primary objective is to derive the maximum commercial value from clinical research through carefully constructed and placed

articles,[30] both by targeting high-profile journals for high market-impact findings as well as by publishing numerous, strategically-related, market-focused papers within lower-profile journals.

Publication planning undermines the clinical trial research process in several ways, as marketing interests influence the research process at multiple different times: during decisions over which trials to conduct, trial design, analytic approach, writing of manuscripts, and whether or not to publish trial findings. However, these decisions are not observable and publication planning is akin to a "ghostly" hand behind the scenes managing and shaping the medical literature.[29]

The earliest exposition of publication planning came from litigation against Pfizer related to sertraline, a selective-serotonin reuptake inhibitor (SSRI) used to treat depression. Documents were identified that suggested the company was tracking and coordinating 85 drafts of manuscripts with the assistance of a medical education and communications company (MECC), including submission dates, journal revision requests, and expected publication dates.[28] Upon publication, few articles disclosed Pfizer's or the MECC's involvement, although documents clearly indicated that authors were not acting independently. This publication planning strategy had great impact as these 85 articles composed the majority of the literature for sertraline and were uniformly positive in their discussion of the medication.[28] Other examples of publication planning have been described among the clinical research strategies for rofecoxib[32] and gabapentin.[27]

Key Messaging—Publication planning is notable not only for managing and shaping the medical literature, but also the eventual message conveyed by the article or series of articles.[29] Often understood as "key messaging," company marketing departments, often in collaboration with MECCs, identify messages or themes that are expected to promote sales and then plan publications around these themes. Such plans include determination of target audiences, tailoring key scientific and clinical communication points, or messages, and timing their release so that the number of articles produced by a publication planning team peaks as the product launches, ensuring that medical professionals are familiarized with the product at a commercially optimal time.[31] The continued rise in the number of MECCs offering "strategic communication planning,"[33] and their close relationship with the pharmaceutical industry,[34] suggests this practice is common.

Ghostwriting and Guest Authorship—Another feature of publication planning is the use of ghostwriting and guest authorship. Guest authoring has been defined as the designation of an individual who does not meet authorship criteria as an author,[35, 36] whereas ghostwriting is the failure to designate an individual who has made a substantial contribution to the research or writing of a manuscript as an author.[35] Both practices undermine the clinical trial research process, crediting investigators with a role in the study not commensurate with their actions in an attempt to convey academic objectivity on a trial. Of note, these external authors rarely have access to the trial data for independent analysis and are only included after the manuscript has been first drafted, when key decisions in the presentation of the data have already been made, including which analyses to present. These practices go beyond investigators being given editorial assistance in drafting a manuscript or managing the references and involve the preparation of a fully drafted manuscript with the data, tables and figures already selected for inclusion.

As an example, we reviewed documents produced as a part of litigation against Merck related to rofecoxib and found that clinical trial manuscripts related to rofecoxib were often authored by employees but often attributed first authorship to academically-affiliated investigators who did not always disclose industry financial support.[32] Similarly, review

manuscripts were often prepared by unacknowledged authors and subsequently attributed authorship to academically-affiliated investigators who often did not disclose industry support.[32] Many other recent examples of ghostwriting and guest authorship of clinical trial manuscripts have been recently described, including among Prempro (conjugated estrogen/medroxyprogesterone) manuscripts sponsored by Wyeth,[37] paroxetine manuscripts sponsored by GlaxoSmithKline through its case study publications for peer review (CASPPER) program,[38] sertraline manuscripts sponsored by Pfizer,[28] gabapentin manuscripts sponsored by Pfizer and Parke-Davis,[27] and warfarin manuscripts sponsored by AstraZeneca.[39]

Selective Publication and Reporting

Selective publication and reporting, which includes ambiguous reporting, undermines the clinical trial research process through the suppression or distortion of trial results. Because industry remains the largest sponsor of clinical trial research, a company's decision to selectively publish trials or report outcomes from a trial has substantial potential to distort the medical literature. These practices are often engaged in to serve marketing interests and enabled by industry ownership of the trial data. Industry decides which clinical trial findings to submit for publication, if any, and the final content of the manuscript, including which analyses. In fact, even among the research contracts between pharmaceutical companies and academic institutions, where academic autonomy is expected, 50% allow industry to draft the manuscript, making content decisions, and 24% give industry the right to use their data tables for a manuscript, as opposed to academic researcher-constructed data tables.[40]

Selective Publication—The practice of not publishing clinical trial results is known as selective publication and can include both delayed publication and non-publication of completed trials. Many prior studies have documented low publication rates of clinical trials, suggestive of selective publication, particularly among industry-sponsored trials.[41–52] For instance, a comparison of published trial articles with trial reports submitted for FDA review found that 31% of antidepressant trials were not published.[43] Another of trial reports submitted to the FDA within new drug applications found 22% of trials were unpublished 5 years after submission and that published trials were more likely to have favorable primary outcomes and less likely to include unfavorable outcomes in published reports.[52] Our examination of completed clinical trials that had been registered in ClinicalTrials.gov, the publicly-accessible, internet-based registry of clinical trials managed by the NLM, found that fewer than half had been published, with the lowest rates of publication among trials primarily sponsored by industry.[51]

Fewer studies have attempted to document delayed publication. One example is the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression [ENHANCE] trial,[53] which compared the effects of simvastatin with those of simvastatin plus ezetimibe among patients with familial hypercholesterolemia on the progression of atherosclerosis. This trial was completed in April 2006, although the findings, which were negative, were not made public until January 2008, when released in the news media.[20] The trial was not formally published until March 2008,[53] but its delayed publication permitted the continued rapid adoption of ezetimimibe[54] without requiring physicians to take into account new, non-supportive evidence.

Selective Reporting—Selective reporting, which involves the partial or incomplete reporting of all clinical trial findings, includes both partial reporting of results from protocol-defined analyses and reporting a secondary outcome as the primary outcome post-hoc. These practices have been previously described as both common and biased.[41, 42, 50] There have been several illustrative examples of selective reporting after litigation

uncovered previously unavailable clinical trial reports.[55] For instance, the published report of study 329 in adolescents sponsored by GlaxoSmithKline claimed that paroxetine was generally well tolerated and effective for major depression.[56] By contrast, internal documents revealed that in study 329, paroxetine was not significantly effective for depression for any of the eight protocol-specific outcomes and was associated with harm.[57] Similarly, a recent comparison of internal company documents obtained during litigation with published reports of 20 trials of gabapentin for off-label indications funded by Pfizer and Warner-Lambert's subsidiary, Parke-Davis, found numerous examples of selective outcome reporting.[58] Critically, trials that presented findings that were not significant for the protocol-defined primary outcome in the internal documents either were not published in full or were published with a changed primary outcome.

Other examples of selective reporting have been described without the use of litigation. For instance, a comparison of published trial articles with trial reports submitted for FDA review for 12 antidepressants found that 37 of 38 studies viewed by the FDA as having positive results were published, whereas, with 3 exceptions, studies viewed by the FDA as having negative or questionable results were, with 3 exceptions, either not published (22 studies) or published in a way that conveyed a positive outcome (11 studies).[43]

Ambiguous Reporting—Ambiguous reporting, which involves the full reporting of relevant findings, but in a way that is misleading, has been received far less attention. Two examples from rofecoxib trials are illustrative. First, Psaty and Kronmal described contradictory representations ofmortality outcomes in two clinical trials of rofecoxib for patients with Alzheimer's disease or cognitive impairment after reviewing the published articles[59, 60] along with internal company analyses made available during litigation.[61] The published articles reported the number of deaths among both subject arms (9 vs. 2 and 41 vs. 20 for rofecoxib and placebo, respectively) without providing statistical analysis and concluded rofecoxib was "well tolerated." In contrast, as is clear from this data, an internal analysis conducted at least three years prior to publication of either trial found 3-fold increased risk of mortality among rofecoxib subjects.

Second, the VIGOR trial,[62] which compared upper GI event incidence among patients with rheumatoid arthritis randomized to rofecoxib or naproxen, also published misleading findings. When presenting pain scores and GI event outcomes, rofecoxib was consistently "handled" as the intervention treatment, such that outcomes were described as rofecoxib users relative to naproxen users. However, when presenting general and cardiovascular safety outcomes, the risk ratios were "flipped" and outcomes were described as naproxen relative to rofecoxib.[63] The risk for myocardial infarction was described as "less common in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent; … relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7)", as opposed to, more accurately, a relative risk in excess of 4.[64] Unfortunately, this "flipping" of the efficacy and safety end points was only one of many problems in the conduct and publication of the VIGOR trial, for which the company, academic collaborators, and medical journal editors all bear some responsibility. The trial lacked a standard operating procedure for collecting cardiovascular adverse events, permitted financial conflicts of interest among scientific advisory board members, and used several methods to obscure the increased risk identified in the trial, such as excluding three cardiovascular events from analyses, performing a misleading post-hoc sub analysis among patients with "indications for aspirin", and offering substantial speculation about the "naproxen hypothesis".[63]

PROMOTING TRANSPARENCY

The practices reviewed highlight the potentially subversive role of industry in clinical trial research, wherein information that is relevant to patients and physicians is obscured, raising concerns about the integrity of the science and the potential for a distorted medical literature. To address these practices, there is a need for policies that promote transparency into the clinical trial research process, so that all relevant information is disclosed to the public, including patients, physicians, regulators, and policymakers, to at least partially mitigate industry's undue influence. Broadly speaking, greater transparency is the process of making public the decisions or actions that were previously made out of the public eye. Three policies hold the greatest promise, but require thorough implementation and oversight: (1) complete public disclosure of research objectives and investigator roles, including study design and authorship contributions, as well as financial relationships; (2) public registration of clinical trials, including study enrollment, main outcomes, and study design; and (3) independent, objective analysis of clinical trial data (Table 2).

Complete Disclosure

Full and complete public disclosure of individuals' and industry's roles and responsibilities in the clinical trial research process, as well as sponsorship of research, is critical for ensuring accountability and responsibility. Progress has already been made toward promoting transparency of investigator relationships and support from industry chiefly through actions of medical journal editors. During publication, disclosure has gradually intensified from requiring investigators to name industry sponsors of their research, to requiring disclosure of all potential financial conflicts of interest by naming companies from which they received payments related to research, consulting or other services, to the International Committee for Medical Journal Editors (ICMJE) recently adopting a uniform form for the disclosure of potential conflicts of interest[65] that simplifies and standardizes financial disclosures. This standardization was particularly useful given the variability among journals in what information was required for disclosure and in what was published. However, in the past decade, other sources of information on financial payments from industry to physicians have materialized. First, individual states, such as Minnesota, Vermont, and Massachusetts, enacted legislation requiring pharmaceutical companies to disclose payments to physicians related to research, consulting, education and other work.[66] Second, initially as a consequence of litigation settlements, pharmaceutical and medical device companies began publicly-disclosing these same payments, most often for service on speakers bureaus or educational honoraria. Finally, as part of the recently enacted Patient Protection and Affordable Care Act, the Physician Payment Sunshine provision requires drug, device, biologic and medical supply manufacturers to publicly report gifts and payments made to physicians and hospitals beginning in 2013. Although this information will provide the most comprehensive information to date with respect to physician payments from industry, one major limitation of the legislation is that payments related to clinical trials or product development are allowed a public disclosure delay of four years or until product approval, whichever comes first. Similarly, product development agreements for "new applications" are also allowed this delay. Therefore, the value of this legislation for promoting transparency with respect to investigator relationships and support from industry will need to be monitored.

Despite recent advances in disclosure of investigator relationships and support from industry, less progress has been made in requiring disclosure of contributions of all investigators, either industry-affiliated or not, who played a role in the design, conduct, and dissemination of a clinical trial. While some of the most prominent medical journals require investigator contributions to be disclosed, and publish this information, many other journals do not. Ideally, a standardized, uniform form, similar to the ICMJE's form for the disclosure

of potential conflicts of interest[65], would be developed, widely adopted, and made publicly available for the disclosure of investigator contributions. Moreover, this disclosure should be adopted not only by medical journal editors, but also by any venue where clinical trial work is submitted or disseminated, including scientific conferences and media releases, as well as IRBs, the National Institute of Health (NIH) or other funders, FDA, and clinical trial registrations. To address the more thorny issues of ghostwriting and guest authorship, all authors should consistently, and explicitly, describe contributions to the research process for all manuscripts, regardless of a journal's requirements. Authors who "sign-off" on or "edit" original publications or reviews should, at a minimum, offer full authorship disclosure, such as, 'drafting of the manuscript was done by representatives from *XYZ, Inc.*; the authors were responsible for critical revisions of the manuscript for important intellectual content.' A uniform and coordinated strategy, adopted by the ICMJE, FDA, NIH and others will be necessary to be successful.

Complete public disclosure of individuals' and industry's roles and responsibilities in the clinical trial research process, as well as in the sponsorship of research, will clarify investigator roles, potential conflicts of interest or sources of bias, and provide more comprehensive information for physicians, patients, and IRBs to consider when evaluating the research. Moreover, more comprehensive disclosure appeals to a sense of professionalism and ethical practice. However, additional work is needed to identify ways to improve the disclosure process. Social sciences research suggests that disclosure actually attenuates skepticism of research conduct, as opposed to raising concerns, when there are potential sources of conflict of interest.[67] At this time, there is no evidence to suggest how disclosure of author contributions or financial conflicts of interest can be most effective. Perhaps disclosures need only be available on the medical journal website, or perhaps published at the end of every article, or perhaps published within an article's abstract. Similarly, there is no evidence to suggest whether disclosure of financial conflicts of interest is sufficient, or if providing additional information is more effective, such as the amount of dollars paid to the investigator or the exact services provided, which may range from Advisory Board service to providing promotional talks.

Clinical Trial Registration

Public registration of clinical trials, including registration of the study design and intervention, enrollment targets and sample size calculation, subject inclusion and exclusion criteria, primary and secondary outcomes, and pre-specified primary, secondary, and subgroup analyses, is critical to ensure that the entire clinical trial research process can be publicly known. Through public registration, trials that had previously been conducted but never published can be found and included in systematic reviews. Moreover, trials that deviate from protocol, reporting a secondary outcome as primary or not reporting certain outcomes, can be identified. Over the past 15 years, several pieces of legislation have required increasingly more information about clinical trials to be publicly registered. First, Section 113 of the 1997 FDA Modernization Act was enacted in the United States in order to provide the public access to information about ongoing clinical trials in which they may be able to participate. The Act required the creation of a public resource for information on studies of drugs, including biological drug products, which treat "serious or life-threatening" diseases and conditions conducted under the FDA's investigational new drug regulations and mandated the collection of specific descriptive information pertaining to each clinical trial. In response, the NLM established ClinicalTrials.gov, a Web-based registry, in 2000 to provide a publicly-available, easily-searchable, on-line source of information for all registered trials, including trials located domestically within the U.S. and internationally.

Then, in September 2007, the FDA Amendments Act (FDAAA) in the United States substantially expanded the registry by now requiring the sponsors of all drug, biologic, and

device trials to register their studies, at inception, in ClinicalTrials.gov (with the exception of Phase I clinical trials). Moreover, it required updating the registry with information on participants and trial results for approved drugs and devices within 12 months of study completion (24 months if the studied drug is currently under review at the FDA); specifically, investigators must report the primary and principal secondary outcome results as well as safety results to ClinicalTrials.gov for inclusion within the publicly-available registry.

Public registration of clinical trials, which will allow comparison of protocol-specified primary and secondary outcomes and planned analyses with published trial findings holds great promise to minimize selective reporting of results. Furthermore, by simply requiring public registration of all trials, selective publication will be more easily identified. However, this legislation only requires registration of trials conducted within the United States or by U.S. investigators and could be circumvented by moving trials to sites outside of the U.S. Furthermore, penalties for not registering trials have yet to be issued. The success of public registration is dependent upon thorough oversight with significant penalties for non-compliance.

Independent Trial Data Analysis

Independent analysis of clinical trial data from publicly-sponsored trials or of approved drugs and devices is necessary not only to validate key findings, but also to ensure objectivity and promote public use of data collected in the spirit of science that contributes to public knowledge. Substantial amounts of clinical trial data routinely collected through industry (and non-industry) supported clinical trials have not been published or have only published selective findings. This vast repository of data could be used to improve public understanding of drug or device efficacy and safety.[68–70]

While post-market summary-level meta-analyses have been conducted for decades, making participant-level clinical trial data available for independent analysis offers several key methodological advantages. First, most clinical trials are conducted expressly to examine drug efficacy for approval or a new indication. However, safety outcomes, as well as other data, are routinely collected within these trials but rarely independently examined. Participant-level data permits the pooling of several trials to analyze rare outcomes. Second, participant-level data allows for greater analytical flexibility, permitting the use of statistical methods to manage trial heterogeneity, as well as the investigation of specific subgroups of subjects. Finally, participant-level data enables pre-specification and re-definition of outcomes, including time-to-event analysis.[71]

Making this data available so that it can be used by independent investigators to complement and corroborate post-market pharmaceutical surveillance done by the FDA and industry will go a long way toward improving the public's health. To promote a central repository for all of this information, this data could be stored and accessed through ClinicalTrials.gov, which is already being expanded to include registration of all trials, as well as trial results, through FDAAA. Data availability plans would need to be negotiated among all trial sponsors, including how much time after study completion until the data could be publicly-accessed. One possibility would be a data application process that would be reviewed by an independent board similar to the Patient-Centered Outcomes Research Institute, with seats for industry, academics, and government officials. In addition, the NIH promotes access to data collected through large awards[72] and several NIH-sponsored observational studies, such as the Health and Retirement Study and the Cardiovascular Health Study, permit public-access to study data, providing a blue print for the creation of similar access to clinical trial data. To be clear, our proposal goes beyond the current debate taking place within the medical journal community about whether industry-sponsored clinical trials need

to be independently analyzed prior to publication. We are suggesting that all trial data be made available for public scrutiny, regardless of whether or where the findings are published.

The importance of independent analysis is illustrated by a cumulative pooled analysis we recently conducted using participant-level data of published and unpublished placebo-controlled trials of rofecoxib produced as a part of litigation.[73] We were interested in whether the drug's cardiovascular risk could have been identified before its withdrawal, despite there being three previously-conducted company-sponsored meta-analyses demonstrating no increased risk.[74–76] We found that pooling clinical trial data demonstrated progressively increased cardiovascular risk as early as December 2000 and reached a P value of 0.05 by June 2001, nearly 3 and a half years before the manufacturer's voluntary market withdrawal.[73] This issue is similarly illustrated by the recent controversy surrounding oseltamavir (Tamiflu). In the process of updating Cochrane Collaborative systematic review, several important research data inconsistencies were found. The drug's manufacturer, Roche Pharmaceutical, although initially declined to share the requested data to resolve these inconsistencies, eventually provided select files that did not fully address concerns.[77] The editors of the *British Medical Journal* write, "In being less than forthcoming with the raw data, Roche has does nothing wrong by current standards. It has done exactly what the current system allows."[77] They later conclude "When vast quantities of public money, and large amount of public trust, are placed in drugs, the full data must be accessible for scrutiny by the scientific community."[77]

Conclusion

Physicians and the public deserve to be in a position to make informed choices about drug and device risks and benefits. Strong, evidence-based practice requires that objective, unbiased research is available to inform individual clinical decisions, systematic reviews, meta-analyses, and expert guideline recommendations. Seeding trials, publication planning, messaging, and ghostwriting, as well as selective publication and reporting of trial outcomes have been used by industry to distort the medical literature and undermine clinical trial research, explicitly by obscuring information that is relevant to patients and physicians. Policies that promote transparency into the clinical trial research process, through improved and expanded disclosure of investigator contributions and funding, comprehensive publicly-available trial registration, and independent analysis of clinical trial data, have the potential to address, at least partially, these subversive practices. These policies will improve accountability among industry and investigators for clinical trial research practice, minimizing the impact of marketing objectives while strengthening the science, which will in turn protect both the integrity of the medical literature as well as the public's health.

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Table 1

Practices that industry has used to obscure relevant information from patients and physicians, undermining clinical trial research and distorting the medical literature.

Practice	Definition
Seeding Trials	Clinical trials of a drug or device among human subjects that are conducted for the purpose of promoting the drug or device and encouraging its use directly to physicians under the guise of their participating as an investigator in a clinical trial, without disclosing the marketing objectives to patients, physicians, regulators, or Institutional Review Board members.
Publication Planning	Organizational and practical work of shaping pharmaceutical companies' data and turning it into medical journal articles to derive the maximum commercial value from clinical research through carefully constructed and placed articles, both by targeting high-profile journals for high market-impact findings as well as by publishing numerous, strategically-related, market-focused papers within lower-profile journals.
Key Messaging	Identification of key messages or themes that are expected to promote drug sales, with subsequent planning of publications around these messages and themes.
Ghostwriting	Failure to designate an individual, in this case an industry employee or an external medical writer, who has made a substantial contribution to the research or writing of a manuscript as an author.
Guest Authorship	Designation of an individual, in this case an academic investigator not employed by industry, who does not meet authorship criteria as an author to confer external objectivity.
Selective Publication	The delayed publication or non-publication of clinical trials that have findings not supportive of a drug or device or that may decrease the commercial value of the product.
Selective Reporting	The partial or incomplete reporting of clinical trial findings that are not supportive of a drug or device or that may decrease the commercial value of the product.
Ambiguous Reporting	The reporting of clinical trial findings that are not supportive of a drug or device or that may decrease the commercial value of the product in a way that is misleading or less likely to attract public attention.

Table 2

Policies that promote transparency and disclosure of all relevant information to the public, including patients, physicians, regulators, and policymakers, attenuating industry's practices that undermine clinical trial research and distort the medical literature.

Policy	Purpose
Uniform and complete disclosure of clinical trial investigator relationships and support from industry, along with industry sponsorship of clinical trial research.	Provide comprehensive information for physicians, patients, and regulators about potential conflicts of interest and sources of bias for consideration when evaluating the clinical trial design, conduct, and findings.
Uniform and complete disclosure of clinical trial investigator contributions to trial design, conduct, and dissemination, for all investigators, regardless of industry affiliation.	Provide comprehensive information for physicians, patients, and regulators about investigator roles and sources of bias for consideration when evaluating the clinical trial design, conduct, and findings.
Public registration of all human subject clinical trials, including registration of the study design and intervention, enrollment targets and sample size calculation, subject inclusion and exclusion criteria, primary and secondary outcomes, and pre-specified primary, secondary, and subgroup analyses.	Identify trials that had previously been conducted but never published, as well as trials that deviate from protocol, reporting a secondary outcome as primary or not reporting certain outcomes, to include and inform systematic reviews and evidence-based practice guidelines.
Making participant-level clinical trial data available for independent analysis.	Independent investigation that complements or validates key findings reported by industry or academic clinical trial researchers, as well as promotion of public use of data collected in the spirit of science that contributes to public knowledge, to improve public understanding of drug or device efficacy and safety.