Promoting Transparency in Pharmaceutical Industry–Sponsored Research

Strong, evidence-based practice requires that objective, unbiased research be available to inform individual clinical decisions, systematic reviews, meta-analyses, and expert guideline recommendations.

Industry has used seeding trials, publication planning, messaging, ghostwriting, and selective publication and reporting of trial outcomes to distort the medical literature and undermine clinical trial research by obscuring information relevant to patients and physicians.

Policies that promote transparency in 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 analysis may address these subversive practices by improving accountability among industry and investigators. Minimizing marketing's impact on clinical trial research and strengthening the science will protect medical literature's integrity and the public's health. (*Am J Public Health.* 2012:72–80. doi:10.2105/AJPH.2011.300187)

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EVIDENCE-BASED MEDICAL practice requires that objective, unbiased research be readily available to clinicians, investigators, and regulators to 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 the pharmaceutical and medical device industries in clinical research and their impact on the medical literature, which is 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 for 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 trial data, the involvement of marketing, inappropriate authorship, and lack of accountability. These and related concerns remain a dominant issue in public and professional discourse.[4–8] We have reviewed several practices that industry has used to distort the medical literature and undermine clinical trial research, explicitly by obscuring information that is relevant to patients and physicians. We subsequently have described 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 has been 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 owing 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 and of various antihypertensives.[14,15] Similarly, comparing a drug to a high-dose active control at a dose high enough to likely lead to greater adverse side effects was described among trials of selective serotonin reuptake inhibitors for depression and antipsychotics for schizophrenia.[16] However, IRBs have made 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 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 online MEDLINE search engine managed by the National Library of Medicine, makes this practice less common as well.

Nevertheless, several related practices remain common and 3 deserve further discussion: (1) seeding trials, (2) publication planning, and (3) selective publication and reporting (see box on the next page). Each undermines the clinical trial research process through acts of commission or omission, by obscuring information from physicians and the public and distorting the medical literature. We have described each practice, using illustrative examples, and discussed 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

Industry Practices to Obscure Relevant Information, Undermine Clinical Trial Research, and Distort the Medical Literature

Practice	Definition
Seeding trials	Clinical trials of a drug or device among human participants 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 data into medical journal articles to derive the maximum commercial value from clinical research through carefully constructed and placed articles by targeting high-profile journals for high market impact findings and by publishing numerous strategically related market-focused articles 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 an article 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 nonpublication of clinical trials that have findings that do not support 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 do not support a drug or device or that may decrease the commercial value of the product.
Ambiguous reporting	Reporting clinical trial findings that do not support 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.

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 nondisclosure prevents patients from making fully informed consent decisions about participation and affects the physician investigators, who are the actual study participants, 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 because they are designed and conducted by marketing. Finally, these trials are often redundant and examine scientific questions that the company has already formally investigated.

As an example, we reviewed documents produced as a part of litigation against Merck related to rofecoxib, a cyclooxygenase-2 inhibitor used to treat osteoarthritis, and found 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 [the trial] was designed and executed in the spirit of the Merck marketing principles.[25(p253)]

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(p253)]

Two other litigation document reviews—in this case examining documents produced as part of litigation against Pfizer and Parke-Davis (a division of the Warner-Lambert Company) related to gabapentin, an antiepileptic 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 the data 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 product marketing.[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 and by publishing numerous strategically related market-focused papers in lower profile journals.

Publication planning undermines the clinical trial research process in several ways, as marketing interests influence the research process at multiple times, potentially including during decisions about the following: which trials to conduct, trial design, analytic approach, article writing, and whether 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 used to treat depression. Documents were identified that suggested the company was tracking and coordinating 85 drafts of articles with the assistance of a medical education and communications company, including submission dates, journal revision requests, and expected publication dates.[28] Upon publication, few articles disclosed Pfizer's or the medical education and communications company's involvement, although documents clearly indicated that authors were not acting independently. This publication planning strategy had great impact because these 85 articles comprised 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 for managing and shaping not only the medical literature but also the eventual message the article or series of articles conveys.[29] Often understood as "key messaging," company marketing departments, often in collaboration with medical education and communications companies, 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 increase in the number of medical education and communications companies offering "strategic communication planning"[33] and their close relationship with the pharmaceutical industry[34] suggest 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 recognized 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 an article 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 included only after the article has first been 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 an article or managing the references and involve the preparation of a fully drafted article 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 articles related to rofecoxib were often authored by Merck employees but often attributed first authorship to academically affiliated investigators who did not always disclose industry financial support.[32] Similarly, review articles 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 articles have been described recently, including among Prempro (conjugated estrogen/medroxyprogesterone) articles sponsored by Wyeth,[37] paroxetine articles sponsored by GlaxoSmithKline through its case study publications for peer review program,[38] sertraline articles sponsored by Pfizer,[28] gabapentin articles sponsored by Pfizer and Parke-Davis,[27] and warfarin articles 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, if any, clinical trial findings to submit for publication and the final content of the article, including which analyses are included. In fact, even among the research contracts between pharmaceutical companies and academic institutions, where academic autonomy is expected, 50% allow industry to draft the article and make content decisions, and 24% give industry the right to use their data tables for an article, 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 nonpublication of completed trials. Many previous studies have documented low publication rates of clinical trials, suggesting selective publication, particularly among industry-sponsored trials.[41–52] For instance, a comparison of published trial articles with trial reports submitted for FDA review showed that 31% of antidepressant trials were not published.[43] Another comparison of trial reports submitted to the FDA within new drug applications revealed that 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 were registered in ClinicalTrials.gov—the publicly accessible, Internet-based registry of clinical trials managed by the National Library of Medicine—revealed 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 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 the news media released them.[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, nonsupportive 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 8 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 revealed 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 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 received far less attention. Two examples from rofecoxib trials are illustrative. First, Psaty and Kronmal described contradictory representations of mortality outcomes in 2 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 along both participant arms (9 vs 2 and 41 vs 20 for rofecoxib and placebo, respectively) without providing statistical analysis and concluded rofecoxib was "well tolerated." By contrast, as is clear from these data, an internal analysis conducted at least 3 years before publication of either trial found threefold increased risk of mortality among rofecoxib participants.

Second, the VIGOR trial,[62] which compared upper gastrointestinal event incidence among patients with rheumatoid arthritis randomized to rofecoxib or naproxen, also published misleading findings. When presenting pain scores and gastrointestinal 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 of 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(p1523)] 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 3 cardiovascular events from analyses, performing a misleading post hoc subanalysis 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 in 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 (see box on the next page).

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. At first, investigators were required by individual journals to name industry sponsors of their research. Then, individual journals began requiring investigators to disclose all potential financial conflicts of interest by naming companies from

Policies That Promote Transparency and Disclosure of All Relevant Information and Attenuate Industry 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 participant clinical trials, including registration of the study design and intervention, enrollment targets and sample size calculation, participant inclusion and exclusion criteria, primary and secondary outcomes, and prespecified 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.	Complement or validate key findings reported by industry or academic clinical trial researchers, as well as promote 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.

which they received payments related to research, consulting, or other services. Currently, the International Committee for Medical Journal Editors, has adopted 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, including 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, biological, 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, a major limitation of the legislation is that payments related to clinical trials or product development are allowed a public disclosure delay of 4 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 the disclosure of investigator relationships and support from industry, less progress has been made in requiring disclosure of contributions of all investigators, whether industry affiliated or not, who played a role in the design, conduct, and dissemination of a clinical trial. Whereas 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 International Committee for Medical Journal Editor'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 in which clinical trial work is submitted or disseminated, including scientific conferences and media releases, as well as IRBs, the National Institutes of Health (NIH) and other funders, the FDA, and clinical trial registrations.

To address the thornier issues of ghostwriting and guest authorship, all authors should consistently and explicitly describe contributions to the research process for all articles, 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, "The drafting of the article was done by representatives from XYZ, Inc.; the authors were responsible for critical revisions of the article for important intellectual content." A uniform and coordinated strategy, adopted by the International Committee for Medical Journal Editors, 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 and 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 a medical journal's Web site, published at the end of every article, or published within an article's abstract. Similarly, there is no evidence to suggest whether disclosure of financial conflicts of interest is sufficient or whether providing additional information is more effective, such as the amount of money 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, participant inclusion and exclusion criteria, primary and secondary outcomes, and prespecified 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 to provide the public with 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, that 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 National Library of Medicine 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 United States and internationally.

Then, in September 2007, the FDA Amendments Act in the United States substantially expanded the registry by requiring the sponsors of all drug, biological, 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.

The 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 the 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 US investigators and could be circumvented by moving trials to sites outside the United States. Furthermore, penalties for not registering trials have yet to be issued. The success of public registration depends on thorough oversight with significant penalties for noncompliance.

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 clinical trials supported by industry (and nonindustry) 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]

Although postmarket 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 permit the pooling of several trials to analyze rare outcomes. Second, participant-level data allow greater analytical flexibility, permitting the use of statistical methods to manage trial heterogeneity, as well as the investigation of specific subgroups of participants. Finally, participant-level data enable prespecification and redefinition of outcomes, including time-to-event analysis.[71]

Making these data available so that independent investigators can use the data to complement and corroborate postmarket 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, these 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 the FDA Amendments Act. 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 blueprint for the creation of similar access to clinical trial data. To be clear, our proposal goes beyond the current debate taking place in the medical journal community about whether industry-sponsored clinical trials need to be independently analyzed before publication. We are suggesting that all trial data be made available for public scrutiny, regardless of whether and 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 3 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 .05 by June 2001, nearly 3.5 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 the Cochrane Collaborative systematic review, several important research data inconsistencies were found. The drug's manufacturer, Roche Pharmaceutical, although initially declining 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 done nothing wrong by current standards . . . It has done exactly what the current system allows.[77(p1322)]

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(1322)]

CONCLUSIONS

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 be available to inform individual clinical decisions, systematic reviews, meta-analyses, and expert guideline recommendations. Industry has used seeding trials, publication planning, messaging, and ghostwriting, as well as selective publication and reporting of trial outcomes, 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 in 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 and the public's health. ■

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Global Alcohol Producers, Science, and Policy: The Case of the International Center for Alcohol Policies

In this article, I document strategies used by alcohol producers to influence national and global science and policy.

Their strategies include producing scholarly publications with incomplete, distorted views of the science underlying alcohol policies; pressuring national and international governmental institutions; and encouraging collaboration of public health researchers with alcohol industry–funded organizations and researchers.

I conclude with a call for an enhanced research agenda drawing on sources seldom used by public health research, more focused resourcing of global public health bodies such as the World Health Organization to counterbalance industry initiatives, development of technical assistance and other materials to assist countries with effective alcohol-control strategies, and further development of an ethical stance regarding collaboration with industries that profit from unhealthy consumption of their products. (*Am J Public Health.* 2012:80–89. doi:10.2105/AJPH.2011.300269)

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THERE IS GROWING RECOGNItion among public health authorities in the United States and globally that the harmful use of alcohol is a global public health issue of serious proportion. At the global level, the most recent estimates attribute to alcohol 4.6% of the global burden of disease and disability, roughly the same level as tobacco. Alcohol use is also responsible for 3.8% of global deaths.[1] In the United States, excessive alcohol use causes 79 000 deaths per year, according to the Centers for Disease Control and Prevention (CDC).[2] In the United Kingdom, the House of Commons Health Committee reported early in 2010 that alcohol consumption has nearly tripled since 1947, and deaths from liver cirrhosis had quintupled between 1970 and 2006.[3] In Russia, more than half of male deaths between the ages of 15 and 54 in the 1990s were caused by alcohol use.[4] In Brazil, nearly 18% of male disability-adjusted life years are attributable to alcohol use; the analogous statistic in Thailand matches that of the United States at 12%.[1] Although female mortality rates attributable to alcohol are lower, a review of the evidence from developing country settings concluded that, throughout the world, although men do more of the drinking, women disproportionately suffer the consequences, through impact on family budgets, domestic violence, and so on.[5]

There is also a growing consensus about how to prevent and reduce alcohol problems. The World Health Organization (WHO) has sponsored periodic research reviews assessing the global research evidence regarding effective approaches. The most recent review, published in 2010, recommends the following interventions: minimum legal purchase age laws, government monopolies of retail sales, restrictions on hours or days of sale, outlet density restrictions, alcohol taxes, random breath testing and lower blood alcohol concentration limits for drivers, administrative suspension of driving licenses for exceeding those limits, graduated licensing for novice drivers, and brief