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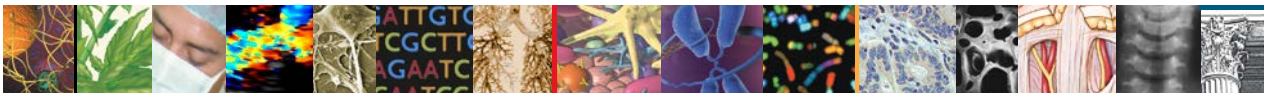
Clinical Trial Transparency - Antidote to Increased Off-label Promotion?

Kevin Outterson
Boston University School of Law



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Perspective

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Clinical Trial Transparency — Antidote to Weaker Off-Label-Promotion Rules?

Kevin Outterson, J.D., LL.M.

This year promises to be an auspicious period for some long-running battles over the dissemination of biomedical research. Some companies seeking more freedom to promote their products have bristled at recent guidance documents from the Food and Drug Administration (FDA) regarding promotion of drugs and devices for off-label uses, claiming that they violate the First Amendment. Simultaneously, industry is divided over calls for increased transparency of clinical trial results. But as the FDA's regulatory authority is weakened by First Amendment challenges, the need for clinical trial transparency becomes more urgent.

In the recent guidance documents, the FDA recommended that scientific articles used for off-label promotion be scientifically sound, come from peer-reviewed journals, and be distributed in unabridged form with the approved labeling and a comprehensive bibliography. Clinical practice guidelines used for marketing should be based on a systematic review of the evidence and "be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups." The FDA also recognized the growing importance of social media, describing the situations in which a company is responsible for comments on Facebook and patient-advocacy websites focusing on specific diseases and treatments. In early June, the FDA expanded this guidance process to include communications about new risk data for existing drugs. The FDA is concerned that companies might use incomplete new information to weaken the impact of warnings on the approved drug label.

Some companies have complained that these rules overly constrain their marketing practices and impermissibly infringe on commercial speech. These claims find some support in recent cases that have undermined the FDA's regulatory authority over drug marketing. The First Amendment has emerged as a potent deregulatory weapon for corporations. Governments increasingly face First Amendment challenges to rules related to the marketing of regulated products, not only from the drug industry but also from companies selling tobacco, alcohol, and processed foods. These industries claim that the government violates a core principle of liberty — freedom of speech — by regulating how food, drugs, alcohol, and tobacco are sold. The FDA issued the new guidance documents with these concerns in view.

In recent years, drug companies have paid billions of dollars

in fines related to off-label promotion. Whether the First Amendment protects this activity remains an open question. The FDA's position is nuanced. Under the law, a drug is viewed as "mislabeled" unless "its labeling bears adequate directions for use." The FDA does not require labels to discuss all possible uses, which would be burdensome to the companies, but only those actually intended by the company. One way to prove this intention is to examine company statements about the drug, including promotional activity. Companies can make any truthful and nonmisleading statement about their drugs, but when they choose to speak about any particular use, the label must bear adequate directions for that use. Speech is frequently used to prove elements of other crimes; examples include perjury, premeditated murder, and conspiracy.

Seen in this light, the recent draft guidance documents do not constrain First Amendment values. They provide safe harbors, listing circumstances in which the FDA will not consider actions to be evidence of intent to sell a drug for a particular use. And the guidance is quite lenient: a company can sponsor biomedical research for an off-label use, refuse to submit that research to the FDA for an expanded label, but nevertheless widely distribute reprints of relevant journal articles to physicians and chat about them on Facebook and other social media. The FDA is keeping a respectful distance from the First Amendment, while gently reinforcing better practices, including peer review and disclosure of conflicts of interest.

If the Supreme Court's interpretation of the First Amendment continues to constrain FDA influence over the dissemination of research, then even greater importance must be placed on improving research quality and providing the support independent research teams need to reanalyze clinical trial data. Studies have highlighted strategic weaknesses in the research enterprise, including failures in peer review, publication bias, bias introduced by sponsors or investigators, and extensive financial relationships.[1]

Transparency is an important tool for addressing these issues, and many stakeholders are working to improve transparency in biomedical research. The International Committee of Medical Journal Editors has adopted standards to improve the quality of the peer-review process, require registration of clinical trials before patient enrollment, and improve disclosure of conflicts of interest. The United States requires advance registration of many clinical trials; since 2007, summary results must also be published. Similar initiatives have been implemented in Europe and beyond, including a global clinical trial registry maintained by the World Health Organization. Advance registration and summary publication are important tools for reducing opportunities for publication bias and making it harder to hide negative studies.

Pressure is now building for two additional data-transparency goals: giving responsible independent researchers access to patient-level data to enable them to replicate studies and perform meta-analyses[2]; and requiring public release of clinical study reports submitted to governments for marketing approval, which have substantial informational value.[3] Companies have traditionally protected these data as trade secrets,[4] but major changes are under way.

In the United States, the FDA requested comments in 2013 on a proposal supporting a limited level of transparency for product-masked patient data. Product masking protects the identity of both the drug and the patient, which limits the data's clinical utility for research. Currently, this effort appears to be on hold, awaiting results from a review by the Institute of Medicine. Meanwhile, transparency initiatives by some companies and legislative action in Europe may have reached the tipping point, with momentum growing for transparency that goes well beyond product-masked data.

Limited patient-level data are now being made available to independent researchers. In May 2013, GlaxoSmithKline opened some of its patient-level data to responsible researchers, with an independent review panel acting as the gatekeeper.[5] Johnson & Johnson followed suit in January 2014, partnering with a group at Yale. These programs are welcome improvements and should expand across the industry.

I believe that transparency should also extend to the clinical study reports submitted to the FDA and other drug-regulatory authorities. On April 2, 2014, the European Parliament adopted reforms to its rules governing human clinical trials, including a key provision requiring delayed release of clinical study reports submitted to the European Medicines Agency. The next day, AbbVie dropped its lawsuit against the agency, which had sought the release of clinical study reports on two AbbVie drugs. Other litigation remains pending, and the European Union may yet weaken these rules, but these events suggest that disclosure of clinical study reports may soon be the norm in Europe.

In public comments on the European reforms, the drug industry raised objections to the release of clinical study reports. Although companies have no trade-secrecy right to hide safety data on medicines, they make a reasonable point regarding the danger of substantial competitive harm from full transparency. Governments offer non–patent-based incentives for special categories of drugs, such as orphan drugs and biologics. These incentives have frequently rested on data exclusivity, prohibiting other companies from using data for regulatory approval purposes. To the extent that transparency disrupts data-exclusivity incentives and the timing of generic entry, both domestically and internationally, the law will need to be adjusted in order to restore the competitive position of the companies. The alternative is to delay data releases until many years after a drug is approved, but neither the progress of science nor public safety should wait for full transparency. The companies will also retain the full force of patent law to block premature generic entry. If this issue is resolved, the onus will be on the industry to articulate why clinical study reports should not be immediately released when a drug is approved.

An audio interview with Professor Outterson is available at NEJM.org

After decades of criticism about bias in the clinical trial enterprise, new norms are being established that promote transparency. Additional transparency is particularly welcome in the United States, since the Supreme Court has increasingly constrained the FDA's ability to regulate off-label marketing activities. In the deregulatory environment fostered by First Amendment challenges, clinical trial transparency is perhaps the best remaining option for informing physicians and protecting patients.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From Boston University School of Law, Boston.

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Putting Quality on the Global Health Agenda

Kirstin W. Scott, M.Phil., and Ashish K. Jha, M.D., M.P.H.

In 2005, after years of persistently high maternal mortality rates, India implemented Janani Suraksha Yojana (JSY), a conditional cash-transfer program in which women were paid to deliver their babies in health care institutions. The program's effect was as profound as it was disappointing: although the rates of institutional deliveries soared, there was no detectable effect on the country's maternal mortality rate.[1]

This paradox — a substantial increase in access to health care services with little improvement in patient outcomes — holds a critical lesson. Universal health coverage has been proposed as a potential umbrella goal for health in the next round of global development priorities.[2] The reasons for focusing on such a goal are compelling: for much of the world's population, access to health care is severely limited and often financially out of reach. Policymakers have responded by developing creative financing plans, workforce training efforts, and other programs that enhance a country's capacity to provide health care services while ensuring financial protection for its citizens. Though these efforts are necessary, lessons from recent interventions that focus primarily on enhancing access — such as JSY in India — remind us that augmenting access will not be enough. In order to improve the health of the world's population, we need to simultaneously ensure that the care provided is of sufficiently high quality, an issue that has garnered far less concrete attention.

Although there is no single definition of high-quality care, the Institute of Medicine describes it as having six key features: it is safe, effective, patient-centered, efficient, timely, and equitable. All these features are important, but there is recent evidence of particularly substantial deficiencies in the first three (see table).