Communicating and Promoting Comparative-Effectiveness Research Findings

Peter J. Neumann, Sc.D.

The comparative-effectiveness research (CER) movement has sparked an important debate about who may communicate research findings, for what purposes, and using what methodologic standards.[1-3] CER is intended to inform discussions about what works in health care. Much of the information comes from research using retrospective databases and quasi-experimental designs rather than randomized clinical trials. The Food and Drug Administration (FDA) prohibits drug companies from using such information to promote pharmaceuticals, requiring that promotions be supported by "substantial evidence" of purported effects (which generally means evidence from two well-controlled trials, though one randomized, controlled trial is permitted in certain circumstances).[1,2]

Pharmaceutical companies have complained about "asymmetry" between the strict rules for their industry and the absence of restrictions for other organizations — including public and private payers and agencies such as the new Patient-Centered Outcomes Research Institute (PCORI) — which are increasingly conducting CER and communicating its results.[3] The counterargument is that permitting drug companies to freely promote CER findings, including those that don't meet the substantial-evidence standard, opens the door for industry to mislead physicians and patients, potentially harming public health and safety.[2] It would also remove incentives for companies to conduct confirmatory trials, effectively allowing them to circumvent the FDA requirements for drug approval.[2] Moreover, there are existing channels for manufacturers to communicate CER findings, even if the data do not meet the substantial-evidence standard. For example, manufacturers can write letters to the editor in defense of public challenges, distribute peer-reviewed articles discussing unapproved uses (with certain restrictions), and respond to unsolicited requests for information.[2] Industry representatives, however, respond that the rules for communication outside of the substantial-evidence standard are vague and that the lack of formal FDA guidance has restricted their actions.[3]

In part, the issue can be addressed with better standards for the conduct and translation of CER. FDA officials recently noted that such standards are a necessary prerequisite to ensuring that comparative-effectiveness information from observational studies will provide credible evidence.[1] Several groups are developing standards for using observational data in CER and, more generally, for including nonrandomized studies in systematic reviews. Eventually, the FDA might be able to determine when such studies meet substantial-evidence requirements.[2] But standards alone are unlikely to suffice. Though the field is improving, judging whether a study based on observational data is of high quality will always be challenging, given unmeasured confounders and investigator choices in design and analysis that can affect results.[2] The advent of CER organizations such as the PCORI, which has a specific mandate to disseminate CER findings, calls for a more immediate response.

A possible step forward would be for Congress to broaden the scope of a legislative provision — Section 114 of the Food and Drug Administration Modernization Act of 1997 — that enables drug companies to promote information related to health care economics that conforms to a broader "competent and reliable scientific evidence" standard rather than the substantial-evidence criterion, as long as the targets of that promotion are restricted to formulary committees or similar entities and the information is directly related to approved indications (see table).[3,4] Extending Section 114 to include CER findings would permit pharmaceutical companies to promote the information using the competent-and-reliable standard, though only to organizations such as health plans. The FDA could use the Federal Trade Commission's definition of competent and reliable scientific evidence, which encompasses evidence based on the expertise of relevant professionals using generally accepted procedures, rather than requiring two well-controlled trials.[3]

Evidentiary Standards and Intended Audiences under Current Law and Proposed Expansion.

Current Legal Authority or Proposed Expansion	Evidentiary Standard	Type of Information	Intended Audience
Food, Drug, and Cosmetic Act	Substantial evidence	Clinical data from randomized, controlled trials	Physician and consumers
Food and Drug Administration Modernization Act, Section 114	Competent and reliable scientific evidence	Health care economic information	Payers
Proposed change	Competent and reliable scientific evidence	Comparative-effectiveness research using observational data	Payers

Expanding Section 114 in this way would reflect a grand bargain of sorts, providing a more flexible evidentiary framework for business-to-business communication of CER findings while retaining key protections. It would open the door to promotion of results from a wider range of CER studies, including those using observational data to draw inferences about patients, settings, and end points (e.g., adherence, hospitalizations) that are of interest to payers and are difficult or impossible for drug companies to include in registration trials.

Of course, the plan is not without risks. There remain concerns that allowing drug companies to promote information about end points that have not been adequately studied could still deceive intended audiences and remove incentives for companies to conduct randomized trials. Historical examples of misleading industry marketing and selective reporting of clinical data are warnings to proceed with caution.[2] The proposal presumes that health plans have the expertise and wherewithal to judge CER information, and the situation should be monitored. In addition, Section 114 has proved to be challenging to regulate and interpret. To date, the FDA has never released any guidance or taken any regulatory action on the matter.[5]

However, the plan would preserve key guardrails for public health. Promotion would be restricted to organizations that retain strong incentives to be informed and wary consumers of drug-company promotions and that increasingly employ their own experts, mine their own data, and request CER evidence from companies, sometimes in the form of dossiers using the Academy of Managed Care Pharmacy Format for Formulary Submissions.[4] The substantial-evidence standard would remain in place for industry promotion targeting physicians or consumers. Product manufacturers would retain powerful incentives to conduct trials on appropriate indications, populations, and comparators, because such research would provide them with labeled claims for general promotion. Furthermore, the new legislation requiring the FDA to regulate CER promotions according to the competent-and-reliable standard could include a directive to the agency to issue guidance about when such promotions amounted to non-misleading information, which would help advance the creation of standards for CER.

A step forward might be to allow pharmaceutical companies a more flexible evidentiary framework for business-to-business communication of CER findings while retaining key protections.

Other mechanisms for exchanging trusted information, such as peer-reviewed publications, would continue to exist, and the creation of additional ones should be encouraged, including government-supported academic detailing of CER findings and the development of ClinicalTrials.gov-type models for observational research (ideally, with FDA- and journal-imposed requirements that designs for observational studies be posted publicly before initiation of a study).[2] The new law could also require disclaimer or disclosure statements when information does not constitute substantial evidence.[3]

The entire debate over the promotion of CER findings has also been thrown for a loop by a

series of recent court decisions, including the December 2012 ruling in *United States v. Caronia*, in which the Second Circuit court overturned a conviction of a drug company sales representative for off-label promotion on the grounds that FDA prohibitions of such promotion infringed the individual's First Amendment right to free speech. *Caronia* continues a judiciary trend toward broadening the definition of protected speech and holds that the government cannot restrict truthful, non-misleading off-label promotion. Conceivably, the FDA will have to establish on a case-by-case basis whether any CER promotion, regardless of its intended audience, is "truthful." However, a great deal of uncertainty prevails, and it may be some time before there is clarity around the issue. In the meantime, expanding Section 114 to include CER could help Congress, the FDA, and perhaps even the Courts to consider and define more clearly the circumstances and audiences for which CER promotion can be truthful and non-misleading.

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From the Center for the Evaluation of Value and Risk in Health, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston.

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