Clinical trials results databases: Unanswered questions

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PUBLIC HEALTH

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Hasty legislation mandating posting will not be enough to ensure public safety.

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Public outcry over pharmaceutical companies' failure to report safety data from research on antidepressants and COX-2 inhibitors has exerted pressure on industry, researchers, and policy-makers to ensure transparent and unbiased reports of clinical trials results (*1*–*3*). One response receiving international attention is creation of clinical trials registries and results databases (*4*). In general, clinical trials registries provide a public record of the nature and eligibility criteria of newly initiated, ongoing, and closed trials. Results databases are public postings of all clinical trials findings, including potentially adverse side effects. Although there has been widespread debate on the rationale and criteria for registries, much of the dialogue (as well as legislation introduced in the U.S. Congress and in more than 20 states) fails to address key questions about results databases (*5*).

The original intent of registries was to inform patients about clinical trials in which they might participate (*6*, *7*). However, their purpose has expanded. The International Committee of Medical Journal Editors (ICMJE) sought to guard against "positive results bias" in publication of clinical trials by limiting acceptance of manuscripts to studies that had been entered into a registry at their inception (*8*). The ICMJE announcement prompted U.S. state and federal legislation [Fair Access to Clinical Trials (FACT) Act has been introduced in the House of Representatives and Senate], proposals from international bodies such as the World Health Organization, and creation of voluntary industry registries (*9*–*14*).

Summaries of and links to publications reporting the results of completed clinical trials are also available from Web sites posted by the U.S. National Institutes of Health (*7*) and the Pharmaceutical Research and Manufacturers of America (PhRMA) (*12*), and a handful of industry registries, but they are not required. However, the FACT Act and some state legislation propose a mandatory linkage.

Implications for Clinical Trials Science

The current legislative proposals call for posting and open access to all raw or summative clinical trials data from successful studies, as well as those that have failed or produced equivocal results or data contradictory to a report submitted for review. However, there has been no discussion about whether the availability of large bodies of data from studies that may or may not have scientific merit will improve or distract from the peer-review process. Moreover, the absence of guidelines for how to include a large body of ancillary data in peer review of submitted manuscripts could compromise actual or perceived fairness of review. Results databases are not a substitute for systematic scientific peer review and scientific rigor.

The Public Library of Science (PloS) recently introduced an open-access journal called *PloS Clinical Trials* that promises to provide peer-reviewed data not affected by "the direction of results, size, or significance" of the trial (*15*). To defray the cost of peer review and open access, the journal charges a fee of $2500 upon acceptance of the article for publication with a nonspecified sliding scale for those lacking sufficient funds. It is too early to tell what effect this will have on the science establishment's ability to maintain and to monitor high standards of research design, analysis, and dissemination. However, lack of emphasis on the direction of results or size, elements critical to good scientific method, risks diluting scientific standards for peer review.

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Participant and Patient Protections

In the United States, subject protections are currently instituted through Institutional Review Board (IRB) review of protocols before implementation and by safety and data monitoring boards during the conduct of clinical trials. Some have argued that access to safety data from previous studies will help potential research subjects evaluate the risks of enrolling in new studies. It is also hoped that public databases will improve prescribing and treatment by helping health-care providers and patients keep pace with rapid advances. However, public databases could compromise such protections.

Ethical and scientific evaluation of the potential for and significance of adverse participant reactions in a clinical trial requires: (i) an understanding of the health status of the participant population, (ii) the types of side effects that were or were not anticipated, (iii) the immediate and long-term health consequences of an adverse event, (iv) evidence of a clear causal relation between the event and the product under investigation, and (v) statistical power necessary to draw conclusions regarding causal relations. Public databases that include constantly updated tables or summaries of adverse events in the absence of such scientific understanding risk raising unmerited public or health provider confidence or concern. Health and safety protection of current and potential research participants can be strengthened through new guidelines for streamlining current safety data monitoring procedures that emphasize reporting of product-relevant anticipated adverse events and more timely review of serious unanticipated adverse events.

Results databases are also not substitutes for safety monitoring of commercially available products. Safety concerns may not be apparent until a commercially approved product is studied in a new patient population, until practitioners have prescribed it to a wider heterogeneous population, or until consequences of product misuse come to light. Although reporting of adverse events is mandatory for marketed products, currently there is no process for evaluating safety data of postmarket products across independently conducted trials or for a national communication channel to encourage and facilitate physician reporting—to companies and the FDA—of serious, unanticipated, and significant adverse events in everyday practice. An active postmarket monitoring interface is essential to long-term understanding of how medical products benefit or adversely affect the public.

Health-Care Practice and Cost

Even in large-scale clinical trials, the validity of results rests on representative sampling, dropout rates, and replication. Practitioners and their professional organizations rely on a system of peer review and FDA approval to help filter multiple sources of information about health products and to establish consensus on standards of care. These data-filtering mechanisms are used by physicians and hospitals to make decisions about health product purchases and by health management organizations to establish criteria for coverage of prescription drugs and medical procedures.

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Pressures from patients for physicians to modify prescribing based on public postings of data that have not been subjected to peer review and regulatory interpretation may lead to premature withdrawal of patients from useful treatment regimens or prescriptions for off-label use of a marketed product. Legislative proposals, like the FACT Act 2005, seek to limit such negative consequences by requiring prominent display of a statement indicating when trials are assessing the safety, effectiveness, or benefit of a use not described in the approved labeling for the drug, biological product, or device. However, this problem may be compounded by proposed government actions calling for nonpromotional language in database postings that prohibit sponsors from providing conclusions about the implications of the data for product efficacy and treatment decisions. Public dissemination of decontextualized results summaries may also exert pressure on the FDA to approve or withdraw products prematurely. The establishment of professional guidelines for the application of database information for prescribing may help address these problems.

Administrative resources required to maintain and monitor results databases may increase the costs of health-care products. Pressure to access constantly changing results databases may also create an unreasonable medical "standard of care," which, in turn, can trigger medical malpractice cases and increase professional liability insurance rates. The relation of clinical trials results databases to product use and purchase must also be considered. What if, for example, preliminary results reported in a database supporting less costly products discourage hospitals from purchasing a proven but more expensive device?

How will health insurance plans react to results databases? Will a single study indicating a negative result of a postmarket product discourage health-care plans from covering its use? Might health-care insurers pressure physicians to switch to less costly medications on the basis of preliminary trials posted on a results database? To provide adequate answers to these questions, health-product stakeholders need to push for cost-effectiveness studies and guidelines for the use of databases in health-care practice, purchase, and insurance coverage.

Industry Sustainability

Sponsors are concerned that failure to post results could be construed as sponsor fraud or negligence; product liability actions could become more frequent. At the same time, manufacturers that do publicize preliminary product findings on mandatory databases might be accused of fraudulently promoting an insufficiently tested product. Posting of results on databases may create undue investor hype. Product manufacturers may have to carry errors and omissions (E&O) insurance to cover this type of exposure, and products liability premiums could be adversely affected. Some have argued that mandatory posting of clinical trials results databases could place companies at risk of violating Securities and Exchange Commission Rules against hyping a drug under FDA review through "forward-looking statements" as defined by the Private Securities Litigation Reform Act of 1995 (*16*). If a company posts positive results from the first study completed and then completes a second one that does not support the first, the company might well be accused of misleading investors.

Premature posting of data from unapproved compounds or off-label usage studies could hamper competition. Posting results on unapproved compounds or new applications of marketed products could erode intellectual property protections. Posting of premarket product trial results could reveal competitively valuable analyses or end points derived from intensive negotiation with FDA and international regulatory authorities. For example, there are rules in the United States, Europe, and other countries that allow generic manufacturers and other applicants to obtain approval through abridged procedures by referencing safety and efficacy data in the public domain. Public posting of raw data or full study reports could be used as a basis for such applications, thereby compromising regulatory exclusivity for marketing authorization holders, hurting investor return, and discouraging research funding.

To ensure scientific integrity, advance public health, and sustain health-care innovation, some U.S.-based and international organizations have proposed creating a "blind" data repository linked to a clinical trials registry. In this model, investigators and/or sponsors would be required to submit their data on project completion, but release into a public database would coincide with article submissions and/or approval by FDA or an international body (*5*, *11*).

Clinical research on drugs, biologics, and medical devices is a multisite, multistate, global enterprise that requires a solution that is national and global. All legislated or voluntary clinical trials results databases must consider implications for harmonization across government and private sponsors, state and federal legislation, global and national studies, and products that are approved or commercially available in some but not all countries (*5*, *17*).

Conclusions

Timely and transparent reporting of clinical trials results is essential to effective health-care decision-making and public confidence. However, policies hastily crafted to assuage public concerns may produce unanticipated problems. Clinical researchers and the pharmaceutical industry must take a leadership role, showing greater willingness to engage with other players. But it is not their responsibility alone. Government policies must take into account protections for public health and industry sustainability. Doctors and hospitals must also provide timely information. Continued dialogue among stakeholders is necessary to ensure that steps taken will enhance scientific and social responsibility and will contribute to the vitality and sustainability of clinical trials research.

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10.1126/science.1119685

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