POLICY FORUM: MEDICINE

Clinical Trials and Industry

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Several disputes between clinical researchers and pharmaceutical manufacturers have highlighted the critical importance of protecting the right of trial subjects to disclosure of risks and the academic freedom of investigators. This article presents some conclusions from a 2-year independent inquiry on such a dispute (*1*, *2*).

In 1996, Toronto hematologist Dr. Nancy Olivieri was conducting two clinical trials of the effectiveness of an iron chelation drug for treatment of transfusion-dependent thalassemia patients. She identified two unexpected risks of the drug: that it was not working effectively in some trial subjects, thus exposing them to heart and liver damage from the iron, then later that the drug itself appeared to be causing liver damage. The trial sponsor and manufacturer of the drug, Apotex Inc., prematurely terminated both trials and issued legal warnings to Dr. Olivieri to prevent her from disclosing these risks to patients or publishing her findings. The dispute between Dr. Olivieri and the company grew to involve the reputations of the University of Toronto and the Hospital for Sick Children (*3*).

Apotex based its legal warnings to Dr. Olivieri on a confidentiality clause in a contract it had with her. The clause gave the company the right to prevent communication of trial data to any third parties, including trial subjects, during the trial and for 1 year after trial termination. University of Toronto policy on contract research expressly allowed such clauses, and in this regard, its policy was similar to policies at many other universities.

Despite the publicity received by this case and others (*4*–*7*), clinical researchers in the United States and Canada are continuing to sign contracts with clauses at least as restrictive. For instance, the confidentiality clause in one of these recent contracts has a sweeping definition of confidential information; has no time limit; and is binding on the heirs, successors, and assignees of the investigator. This clause also stipulates that, "[the investigator] hereby consents to [the sponsor] seeking and obtaining injunctive or other equitable relief" [(*1*), p. 79].

Universities and their teaching hospitals should ensure that no contract for clinical research contains clauses preventing researchers from disclosing risks. Relevant government agencies also should take action to require nationwide disclosure standards. These are needed to cover trials done outside academic settings, as well as to prevent a "race to the bottom" in which institutions with less stringent disclosure requirements may be selected by industrial sponsors. As an additional precaution, consent forms and contracts with sponsors should provide explicit written assurance that any unforeseen risks identified during the trial will be disclosed to trial subjects. While waiting for uniform standards to be adopted by institutions or imposed by government agencies, investigators themselves should refuse to sign contracts with confidentiality clauses that could be used to impede them in fulfilling their ethical and legal obligations.

In March 2001, the University of Toronto and all eight of its affiliated teaching hospitals implemented a new policy for industry-sponsored clinical research, intended to disallow contract clauses that could be used to prevent disclosure of risks. The University's Dean of Medicine, David Naylor, published a review of the successes and limitations of the new policy in its first year of operation. He reviewed 152 new research contracts and reported that, in most cases, sponsors accepted the new policy. Only two sponsors refused to sign agreements without such clauses (*8*).

Dean Naylor noted several areas where improvements are still required, for instance, standardization of the allowed period for publication delays and the circumstances for allowing delays across all centers in a multicenter trial. The process to be followed when a sponsor unilaterally terminates the funding or the trial remains to be defined. He acknowledged that arbitration as a procedure for resolving disputes between investigators and sponsors is unacceptable where risks to patient safety are at issue, because no arbitrator can overrule an investigator's ethical obligation. Further, he said that this aspect of the new policy is being revisited.

In the long term, inappropriately restrictive confidentiality clauses can be disadvantageous to industrial sponsors, as a result of considerable adverse publicity. For instance, Apotex and Knoll Pharmaceuticals were criticized in a documentary broadcast by the CBS television network for using confidentiality clauses to suppress adverse findings on their drugs (*9*), and Apotex was criticized in a weekly news magazine (*10*). The actions of both companies were also the subject of commentaries in scientific journals (*11*, *12*).

Industry sponsorship for clinical trials is necessary and valuable in many instances. However, researchers and institutions may have to deal with significant conflicts of interest. Pharmaceutical companies are more powerful than individual researchers, so it is essential that institutions live up to their responsibilities to protect academic freedom and the public interest (*13*, *14*). Editors of leading medical journals have also recently instituted a rigorous policy of safeguarding against conflicts of interest (*15*).

Institutions performing research have a responsibility to protect human subjects (*16*). In addition to robust policies and practices governing research, this requires adequate resources for research ethics boards (institutional review boards) and vigilant defense of investigator independence by administrators. Our society depends on the voluntary participation of citizens in clinical trials to make progress to better treatments. We will all lose if that trust and participation are depleted.

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References and Notes

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