

The above letters were referred to the authors of the article in question, who offer the following reply:

*To the Editor:* The letters from Drs. Rosenblatt and Ellsworth seem to challenge the science and ethics of the Advisory Board and investigators of the Clinical Experience Network (CEN), HLS Clinical Systems, and the peer review process of this *Journal*. It should be noted that prior to submitting these letters, neither Dr. Rosenblatt nor Dr. Ellsworth made an attempt to contact any member of the CEN Advisory Board to seek clarification of the issues about which they have written. It should also be noted that all three of the published papers<sup>1-3</sup> challenged in these letters passed the peer review rigors of *JABFP*; we believe they demonstrate the contribution practicing family physicians can make to the medical literature.

It is our belief that family physicians need to be involved in clinical research so they can help evaluate pharmaceutical products under the actual conditions of clinical use in the "real world" of family practice. Toward this goal, the Clinical Experience Network in Family Practice was created by family physicians to serve family physicians. The hundreds of family physicians who have participated as investigators in these studies have worked hard to collect data on several widely used pharmaceutical products under these "real world" conditions. The Food and Drug Administration has stated four criteria to distinguish between promotional and scientific activities:

1. Independence
2. Objectivity
3. Fair balance
4. Scientific rigor

Phase III clinical studies conducted by pharmaceutical companies for new drug applications must adhere to these four criteria. In conducting Phase IV (postmarketing) studies in the Clinical Experience Network, we also have tried to adhere to these four criteria. With this framework in mind, we will examine how CEN lives up to these standards and then address the specific issues raised by Drs. Rosenblatt and Ellsworth.

The *independence* of the studies performed by CEN is established by HLS Clinical Systems and the Family Practice Advisory Board. These five board-certified family physicians, each a past president of either the AAFP or ABFP (in some cases both), along with a pharmacotherapy specialist member, are empowered with the complete responsibility and authority for study design, review, and approval of all program aspects. A specialist consultant in each therapeutic area to be examined is selected to assist development and execution of each study. The credibility of these physicians is at the heart of CEN.

*Independence* is further maintained by separating the activities of the Board from the sponsoring company.

Once funding has been provided to CEN, the manufacturer acknowledges contractually, in writing, that the study is not designed to support promotional efforts for its product and that it is, in fact, an independent clinical study. Further, the manufacturer agrees in writing that only FDA-approved drugs will be studied for approved indications.

Each of the several hundred investigators participating in each study is identified by name and location. Their *independence* and credibility further contribute to the scientific independence of CEN. One major point of distinction between CEN and other manufacturer-sponsored studies is that in CEN, as data are collected, stored, and analyzed through HLS Clinical Systems, the manufacturer neither possesses the raw data nor conducts the analysis. This is not the case with most other manufacturer-sponsored Phase III or Phase IV multisite studies.

*Objectivity* is maintained in CEN studies throughout the process of data collection, entry, verification, analysis, and reporting. The objectives and methods outlined at the start of the study are maintained throughout and utilized at the end of the study. Each study provides more than 24 references of published papers, which provide a framework for the reader to use in evaluating the study results. Additional layers of objectivity, before the paper reaches the reader, are provided by the Advisory Board and the reviewers for this *Journal*.

Some of the questions raised by Drs. Rosenblatt and Ellsworth appear to be issues of *fair balance*. The reports from CEN are both fair and balanced. CEN reports statistical analysis of the data submitted by the investigators. In some cases, these data have not been complimentary to the sponsoring manufacturer. In fact, our commitment is to publish data as reported regardless of the impact on the grantor's product image. In the CEN antihypertensive trial,<sup>2</sup> for example, we reported an incidence of constipation with verapamil of 17 percent versus the manufacturer's FDA-approved package labeling for constipation at an occurrence rate of 7.3 percent. In the CEN antihistamine trial,<sup>1</sup> we reported that the two agents were more similar than different in patient response.

With regard to *scientific rigor*, various techniques have been employed in the design of each study. The inherent strengths of CEN study designs are the involvement of large physician-patient populations and the actual conditions of clinical use, contrasted with smaller, tightly controlled Phase III clinical studies. CEN studies have Investigational Review Board approval and rigid study protocols. Physicians must adhere to the protocol when enrolling patients. In each published study, study design and methodologies are clearly articulated to show the steps the Advisory Board and the investigators have taken to eliminate bias.

The recent CEN paper on low high-density lipoprotein cholesterol and other coronary heart disease risk factors highlights the demographic characteristics

of patients participating in a comparative study comparing the lipid-lowering effects of diet and exercise versus diet, exercise, and gemfibrozil.<sup>3</sup> The study is not epidemiological, nor is it "billed" as such, as Dr. Rosenblatt incorrectly states. The paper discusses the demographics of patients enrolled in a dyslipidemia study. There is no mention in this paper of efficacy, safety, or any other claim for gemfibrozil. Dr. Rosenblatt's opinion that the paper is an "advertisement" because it is sponsored by a manufacturer is surprising.

Approximately 80 percent of all drug research in the United States is funded by drug manufacturers. The sponsor's name in this case, as in the case of all CEN studies, is prominently and appropriately displayed. Such identification is consistent with the representation medical journals usually give to manufacturer-sponsored studies.

The Family Practice Clinical Experience Network was designed to study products in actual conditions of clinical use and, thereby, to seek to establish some learnings that could help to add resolution and perspective beyond the learnings of restricted Phase III clinical studies. The primary criterion for investigators in this network is board certification in family practice. Several thousand physicians were invited to register with CEN, and indeed about 1500 chose to do so. As each study is initiated, physicians in the network are invited to participate until the target number of investigators is secured. To date, some registered physicians have participated in all three studies, and some have participated in none. From time to time, additional physicians are invited to join the network.

CEN has gathered extensive information detailing the individual practices of these physicians. In the aggregate, CEN has the potential to make an adequate representation of family practice and the patient population in the United States. But the actual mix of investigators who enroll for a particular study varies and sometimes may create disproportionate patient characteristics. For example, in the low high-density lipoprotein cholesterol study, Table 5 makes it clear that 94 percent of the patients in the study were white and 4 percent black.<sup>3</sup> This representation is not accurate for population demographics in the United States but does accurately reflect our study population. This type of skew is inherent in many study populations and is an important criterion for readers to use in evaluating the data presented.

Concerning the study's inclusion and exclusion criteria, the methods and patient selection sections of the paper are quite clear. Further, there is more information provided in this paper about the demographics of the participating physicians than is usually published in a scientific paper (e.g., 49 states and the District of Columbia are represented, 13 percent of physicians are in industrial settings, 9 percent practice in health maintenance organizations, 8 percent in

neighborhood clinics, and 22 percent in teaching hospital environments).

The Advisory Board of CEN received compensation from HLS Clinical Systems for the services they provided in constructing and conducting this study. Further, all of the 327 investigators received a modest compensation for the services they performed in enrolling patients in this trial. It is usual and accepted practice to reimburse investigators for the services they provide in enrolling patients and collecting data. Frankly, most of the investigators who participated in this study were quite upset that their remuneration was disproportionately low for the amount of work they had to do. Any suspicion that people were overly compensated to participate in this study can be laid to rest by discussing the effort versus compensation ratio with the investigators. Further, there are no financial links between the Advisory Board, the investigators, and CEN beyond compensation for efforts related to each clinical study. We know of no financial link between any of the investigators and the sponsoring companies.

The Clinical Experience Network (CEN) is a registered trademark owned and operated by HLS Clinical Systems, a subsidiary of Health Learning Systems, Inc. For 21 years, Health Learning Systems, Inc., has been in the business of producing postgraduate continuing medical education (CME) courses for physicians. Two of their most recent multi-year CME programs were sponsored and accredited by the University of Washington, the home institution for Drs. Rosenblatt and Ellsworth.

Most of the questions raised in these two letters focus on whether bias has been injected into these studies because they are funded by pharmaceutical manufacturers. In fact, virtually all Phase II and Phase III clinical trials are funded by drug companies. To our knowledge, neither the FDA, nor the American Medical Association, nor any other organization has discouraged Phase IV clinical studies sponsored by manufacturers. To the contrary, these organizations encourage industry to sponsor clinical studies and, in particular, Phase IV clinical studies if and when such studies adhere to the standards of independence, objectivity, fair balance, and scientific rigors. The FDA increasingly recognizes the value of Phase IIIB and IV trials. Indeed, such trials were recently emphasized by Dr. Peck of the FDA at the annual meeting of the American College of Clinical Pharmacy in Minneapolis, MN, in August 1991 as an area of needed pharmaceutical research.

In his letter, Dr. Ellsworth implies that the lipoprotein paper "... pushes HDL as an additional risk factor" and is promotional. It should be noted that Ernst J. Schaefer, M.D., a member of the National Cholesterol Education Program, was actively involved as a consultant with this study and specifically with the construction of this paper. Many other informed physicians, such as William Castelli, M.D., Director of the Framingham Heart Study, publicly

support the position that HDL is a significant cardiovascular risk factor. With regard to Dr. Ellsworth's suggestion that a less expensive H<sub>1</sub> antihistamine should have been studied in CEN's antihistamine report, the Board respects this opinion and would encourage him or any other clinician-researcher to conduct such a trial in an equally large and geographically diverse population. We believe, however, that our model of a Phase IV project comparing head to head the two new drugs in a new class of antihistamines is in and of itself a meaningful contribution. Nowhere did we encourage or "teach" practitioners to use the nonsedating antihistamines rather than other antihistamines.<sup>1</sup>

Dr. Ellsworth's comment that his "local Searle pharmaceutical sales representative" inaccurately emphasized certain sections of the hypertension study is unfortunate. It is unrealistic to think that CEN can control the use of data that this *Journal* or any other journal puts into the public domain.

Dr. Ellsworth has stated in his letter that "all of us involved in the design, analysis, and publication of research should maintain the highest possible vigilance to prevent commercial intrusion into the scientific enterprise." It should, therefore, be most surprising to the readers of *JABFP* to learn that Dr. Ellsworth is the lead author of at least two publications funded by industry. Furthermore, two of these publications were funded by companies he is now calling into question: Searle Pharmaceuticals, Inc., and Parke-Davis, Division of Warner-Lambert Company. The complete references for these studies are included at the end of this letter.<sup>4,5</sup> The Advisory Board of CEN is not calling into question Dr. Ellsworth's science or ethics. We are interested to know, however, just how he distinguishes between conflicts of interest in manufacturer-funded studies in which he participates and studies funded by the same manufacturers in which he does not. Has he considered the possibility that a sales representative somewhere may be using his paper<sup>5</sup> to defend disopyramide?

Drs. Rosenblatt and Ellsworth have raised many questions about CEN. Some of the information provided here to answer them has not been published specifically before, but much of it is self-evident from the published papers. Indeed, many of the questions raised by Drs. Rosenblatt and Ellsworth are not questions at all but accusations against the integrity of the advisors and investigators of CEN and the editors of this *Journal*. This type of attack is not consistent with the legitimate, scientific critique by which investigators and readers can build on each others' learnings. We know of no other accusations from any other physicians at any other universities directed at CEN during the 5 years it has been conducting studies. The few unsolicited comments that have been received were positive and encouraged the continued involvement of family physicians in conducting clinical studies on drugs in actual conditions of clinical

use. The professionals involved with the Clinical Experience Network reaffirm their support for the peer review process of *JABFP* and the CEN investigative process.

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2. Managing hypertension in family practice: a nationwide collaborative study of the use of four antihypertensives in the treatment of mild-to-moderate hypertension. A report from CEN. *J Am Board Fam Pract* 1989; 2:172-90.
3. Low high-density lipoprotein cholesterol and other coronary heart disease risk factors in patients with total cholesterol levels greater than 5.17 mmol/L (200 mg/dL) in family practice. A report from CEN. *J Am Board Fam Pract* 1991; 4:285-97.
4. Ellsworth AJ, Christensen DB, Volpone-McMahon MT. Prospective comparison of patient tolerance to enteric-coated vs. nonenteric-coated erythromycin. *J Fam Pract* 1990; 31:265-70.
5. Ellsworth AJ, Horn JR, Raisys VA, Miyagawa LA, Bell JL. Disopyramide and N-monodesalkyl disopyramide in serum and breast milk. *DICP* 1989; 23:56-7.

## Editor's Comment

The above Letters to the Editor raise concerns about the process of Phase IV drug studies as represented by recent articles in *JABFP*. The preceding letters and response illustrate a myriad of procedural and process points at which either perceived or actual conflicts of interest could occur during Phase IV drug monitoring studies. The foregoing letters also indicate the need to communicate openly the process of Phase IV drug studies in order to allow readers of published reports to assess and interpret their findings. In view of the importance and complexity of the many issues involved, our usual space limitations for editorial correspondence have been relaxed in this instance in order to facilitate a full response by the Advisory Board of the Clinical Experience Network, the organization involved in all three studies called into question.

There is an important place for collaborative research in primary care and family practice settings. The Clinical Experience Network has been organized to facilitate involvement of practicing family physicians in collaborative research and so