What About the Role of the US Food and Drug Administration?

To the Editor:

As a professional couple with one half in the world of human subjects’ protection and the other half in the world of academic pulmonary medicine, we read the article by Miller and Shorr1 and the accompanying editorial by Perkins2 with great interest. The article, in the April 2002 issue of CHEST, elucidated the many challenges faced by all of us who conduct research involving human subjects. The authors have brought into focus the ethical challenges presented to the investigator, the institutional review board (IRB), and the sponsor. Although we agree with the authors regarding the problems that they have identified, we suggest that the responsibility for the problems is not limited to the three groups they have identified. We would like to point out some of the inherent and fundamental problems of industry-sponsored randomized clinical trials as they are currently conducted.

The current practice is that industry (with some input from expert consultants) designs clinical trials, the US Food and Drug Administration (FDA) reviews them, and then the sponsor then seeks sites for these trials. As Miller and Shorr1 point out, clinical trials have seen a tremendous change in recent times, moving away from academic medical centers and toward private practice settings. The scrutiny of IRB applications for these trials is different given the context of an independent IRB relative to the academic IRB. There is a potential and very real problem of “IRB shopping” with the obvious benefit that sponsors can have clinical trials conducted, unopposed and without modification. IRBs, both local and independent, are under extreme pressure to review protocols quickly and without requesting modification. By contrast, there is a strong tradition and clear need for local control of IRBs so that their actions reflect the communities that they serve. However, Miller and Shorr1 have pointed out the universal nature of the ethical dilemma confronting the investigators, the IRB, and the sponsor. Obviously, these groups did not meet this ethical challenge in the mometasone trial.

In this context, such review standards and, in fact, this level of review would be more appropriate at the level of the FDA. At the present time, the role that the FDA plays in the risk/benefit analysis for the subject is ambiguous. This realization leads to a variety of troubling questions. What was the role of the FDA in allowing a study such as the mometasone trial to proceed? In general, what kind of review does an investigational new drug (IND) application undergo? Is it reviewed by experts in the area of study? Does the FDA consider whether the protocol meets current guidelines for the treatment of the condition under study, or does the FDA see this as the responsibility of the sponsor or the local IRB?

Our local IRB is frequently told by sponsors that we are the only IRB that has issues with a particular protocol. These issues usually relate to our concerns with including a placebo arm, or with withdrawing or withholding proven treatment. Industry-sponsored clinical trials that do not pass ethical muster or put patients at unjustifiable risk should be stopped at the FDA review. They should be rewritten according to currently accepted guidelines for the treatment of the condition under study, and according to regulations meant to protect any vulnerable subjects who might be included.

At national IRB meetings last year (Public Responsibility in Medicine & Research), Robert Temple, MD, of the FDA board-certified pulmonologist or internist in a similar malpractice action. The simple use of spirometry would have made the defense much easier.

John Hutchinson introduced spirometry in 1846.1 Some time ago, noted physiologist Joseph Milic-Emili wrote on 150 years of blowing, citing the work of Hutchinson, who coined the term vital capacity, and Tiffeneau of Paris, who added the timed vital capacity (ie, FEV1) to spirometry.2

Today, the National Lung Health Education Program recommends spirometry for all smokers ≥ 45 years old and anyone with dyspnea on exertion, chronic cough, mucous hypersecretion, or wheeze.3 Certainly the patient had all of these. The National Asthma Education Program has recommended spirometry in the evaluation of asthmatics for more than a decade.4 Thus, spirometry has to become the standard of care.

Physicians who treat asthma, COPD, and other pulmonary disorders for which steroids may be required will be well advised to “blow their defense” in the form of doing spirometry in conjunction with the initial patient assessment and for documentation of responses to therapy. The use of spirometry is a requirement for the initial evaluation of patients with both obstructive and restrictive ventilatory disorders. It is key to monitoring responses to therapy. The simple use of spirometry would have made the defense much easier.

The issue of aseptic necrosis of the femoral head has been commented on for some time.5–7 It is not clear, however, if aseptic necrosis in patients treated with corticosteroids represents a drug complication, a complication of the disease process, or both.5–7 It is interesting that in 1995, a Massachusetts Supreme Court ruling (Freecourt vs Frederic, 355 Mass 679) held that the risk of acquiring aseptic necrosis from long-term prednisone use was so negligible that the “informed consent” issue should not be used. Simple spirometry is a requirement for the initial evaluation of patients with both obstructive and restrictive ventilatory disorders. It is key to monitoring responses to therapy. The use of spirometry will also help avoid trips to the courthouse. So always remember to blow your defense!

Thomas L. Petty, MD, Master FCCP
Denver, CO

Correspondence to: Thomas L. Petty, MD, Master FCCP, 1850 High St, Denver, CO 80218; e-mail: TLPdoc@aol.com

REFERENCES

1 Hutchinson J. On the capacity of the lungs, and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer. Medico-Chirurgical Transactions (London) 1846; 29:137–161


suggested that the agency preferred to allow protocols to have broad inclusion and exclusion criteria so as not to limit multicenter trials. He saw narrowing of inclusion and exclusion criteria to make a study safe as the responsibility of the IRB. At the same IRB meeting, a representative of the pharmaceutical industry was quick to point out that academic IRBs were a problem for industry, and they would prefer that independent IRBs review all multicentered trials. The implications of this latter statement are obvious. However, the suggestion of the FDA that narrowing criteria should be done at the local IRB feeds this somewhat dysfunctional relationship. The federal government has now begun to realize that IRB shopping is a real phenomenon. Currently, proposed regulations to prohibit IRB shopping are available for public comment. However, prohibiting IRB shopping alone will not resolve the current problems involving the clinical trials industry that lead to conducting trials such as the one reviewed and analyzed by Miller and Shorr.1

Unquestionably, unethical clinical trials have been funded by sources other than industry, and have been approved by local IRBs, including academic IRBs. National Institutes of Health-funded studies have also failed the risk/benefit analysis.

In this time of heightened public awareness of the shortcomings of the human subjects’ protection process, we would argue that rigorous risk/benefit analysis should be applied before protocols reach the local IRBs. In this way, we can help prevent local conflicts of interest and ensure that research is conducted at a standard deserving of the public trust.

Barbara G. Bigby, MA
Scripps Clinic
La Jolla, CA
Timothy D. Bigby, MD
San Diego VA Healthcare System and
the University of California, San Diego
San Diego, CA

Correspondence to: Barbara G. Bigby, MA, Office for the Protection of Research Subjects, Scripps Clinic GEN3, 10666 N Torrey Pines Rd, La Jolla, CA 92037

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Errata

In the September 2002 issue, the book review of Cancer of the Lung: From Molecular Biology to Treatment Guidelines (CHEST 2002; 122:1108–1109), by Albert Miller, contained an error. On page 1109, the last sentence of the fourth paragraph should read “This is fortunate, since T3N0M0 is not included in the former, and stage IV is erroneously defined as any T, any N, M0.” Also the “important article by Henschke” is referenced as: Henschke CI, McCauley DI, Yankelovitz DF. Early Lung Cancer Action Projection: overall design and findings from baseline screening. Lancet 1999; 354:99–105.

In the August 2002 issue, the article, “IV Magnesium Sulfate in the Treatment of Acute Severe Asthma: A Multicenter Randomized Controlled Trial” (CHEST 2002; 122:489–497) by Silverman et al, contained editing errors in study site affiliations. The affiliations should read as follows:

*From the Department of Emergency Medicine (Drs. Silverman and Mancherje), Long Island Jewish Medical Center, New Hyde Park, NY; Department of Emergency Medicine (Dr. Osborn), Lincoln Hospital Medical Center, Bronx, NY; Department of Emergency Medicine (Dr. Runge), Carolinas Medical Center, Charlotte, NC; Department of Emergency Medicine (Dr. Gallagher), Jacobi Hospital Medical Center, Bronx, NY; Department of Emergency Medicine (Dr. Chiang), Bellevue Hospital Medical Center, New York, NY; Department of Emergency Medicine (Dr. Feldman), Boston City Medical Center, Boston, MA; Department of Emergency Medicine (Dr. Gaeta), St. Barnabas Medical Center, Bronx, NY; Department of Biostatistics (Dr. Freeman), Montefiore Medical Center, Bronx, NY; Department of Biostatistics and Epidemiology (Dr. Levin), Columbia University School of Public Health, New York, NY; and Division of Pulmonary and Critical Medicine (Dr. Scharf), Department of Medicine, Long Island Jewish Medical Center, New Hyde Park, NY.

The current affiliation information for Drs. Osborn, Runge, Gallagher, and Gaeta is correct.