

ceutical companies, as part of their efforts to obtain licensing approval, perform most trials of anti-HIV drugs. Consequently, researchers purposely avoid recruiting marginalized populations (such as members of minority groups, substance abusers, or homeless persons) to clinical trials because they believe that poor compliance is common in these groups. Many obstacles to participation by such patients (e.g., homelessness, lack of transportation, limited income, lack of child care, and active drug use) are probably surmountable and, more important, in many studies have not predicted poor compliance.¹⁴ Many other factors are also related to adherence, including fluency in English, the level of functional health literacy (a measure of a patient's ability to read and comprehend written information and to perform numerical tasks related to health care),¹⁵ the complexity of the medication regimen, and the efficacy of the regimen. In clinical practice, physicians have to assess each patient's understanding of the prescribed regimen or tailor the regimen to fit the lifestyle of the patient.¹⁴ However, most clinical trials are not designed to deal with these issues, so the population involved in studies rarely mirrors the full spectrum of patients who are likely to receive the treatment. As a result, many trials of antiretroviral drugs do not provide information on how to use the medications in routine clinical practice.

Finally, investigators have a narrow view of the sort of person who makes a good participant in an HIV-related clinical trial: a white, college-educated, employed, housed, homosexual man. As a result, they have a more difficult time recruiting patients for such trials. In part, recruitment is difficult because many drugs are already available, combination therapy works, and the health of HIV-infected patients is improving. Many patients are reluctant to enroll in new trials, and their physicians, many of whom have a "let's wait and see" attitude, do little to encourage them. But the battle is far from over. The scientific and health care communities must continue aggressive efforts to educate patients with HIV infection about clinical trials and to motivate and encourage them to participate in such trials. In order to provide generalizable results, trials must involve men and women, both homosexual and heterosexual, of all racial and ethnic groups, irrespective of their financial circumstances.

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REFERENCES

1. Svensson CK. Representation of American blacks in clinical trials of new drugs. *JAMA* 1989;261:263-5.
2. National Institutes of Health. NIH guidelines on the inclusion of wom-

en and minorities as subjects in clinical research. *Fed Regist* 1994;59:14508-13.

3. Food and Drug Administration (FDA) Modernization Act of 1997 (FDAMA or the Act), Pub. L. No. 105-115 (November 21, 1997).

4. Gifford AL, Cunningham WE, Heslin KC, et al. Participation in research and access to experimental treatments by HIV-infected patients. *N Engl J Med* 2002;346:1373-82.

5. Shapiro MF, Morton SC, McCaffrey DF, et al. Variations in the care of HIV-infected adults in the United States: results from the HIV Cost and Services Utilization Study. *JAMA* 1999;281:2305-15.

6. Shavers VL, Lynch CF, Burmeister LE. Factors that influence African-Americans' willingness to participate in medical research studies. *Cancer* 2001;91:233-6. [Erratum, *Cancer* 2001;91:1187.]

7. el-Sadr W, Capps L. The challenge of minority recruitment in clinical trials for AIDS. *JAMA* 1992;267:954-7.

8. Stone VE, Mauch MY, Steger K, Janas SF, Craven DE. Race, gender, drug use, and participation in AIDS clinical trials: lessons from a municipal hospital cohort. *J Gen Intern Med* 1997;12:150-7.

9. Smedley BD, Stith AY, Nelson AR, eds. Unequal treatment: confronting racial and ethnic disparities in health care. Washington, D.C.: National Academy Press, 2002.

10. van Ryn M, Burke J. The effect of patient race and socio-economic status on physicians' perceptions of patients. *Soc Sci Med* 2000;50:813-28.

11. Corbie-Smith G, Thomas SB, Williams MV, Moody-Ayers S. Attitudes and beliefs of African-Americans toward participation in medical research. *J Gen Intern Med* 1999;14:537-46.

12. Crawley LM. African-American participation in clinical trials: situating trust and trustworthiness. *J Natl Med Assoc* 2001;93:Suppl:14S-17S.

13. Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clin Infect Dis* 2002;34:1115-21.

14. Fogarty L, Roter D, Larson S, Burke J, Gillespie J, Levy R. Patient adherence to HIV medication regimens: a review of published and abstract reports. *Patient Educ Couns* 2002;46:93-108.

15. Schillinger D. Improving the quality of chronic disease management for populations with low functional health literacy: a call to action. *Dis Manag* 2001;4:103-9.

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IRB REFORM

WE have come a long way since the 1960s, when ethical questions about research involving human subjects brought the issue to national attention. Nonetheless, the current system for safeguarding people who volunteer for clinical trials is under stress because of the unprecedented growth in clinical research.¹⁻³ Since 1995, federal funding for research has more than doubled. From 1997 to 2000, the estimated number of participants in federally funded research increased from 7 million to almost 12 million⁴ (and Seto B: personal communication). Privately sponsored clinical research has grown at a similar pace.⁵ To paraphrase Snyderman and Holmes, as our ability to discover expands, we must be ready for the increasingly dominant role of clinical research in medical practice.⁶

Two articles in this issue of the *Journal* examine current efforts to improve the system for reviewing research protocols. Christian et al. describe a central review process for multi-institutional studies that allows institutional review boards (IRBs) to focus on

local considerations and that ultimately results in greater access to treatment trials.⁷ Steinbrook, in a sequel to his report on the events following the death of a healthy volunteer at Johns Hopkins University Medical Center,⁸ discusses the status of efforts to improve the system for protecting research subjects.⁹

Trials involving investigational drugs and devices are generally subject to the regulations of the Food and Drug Administration (FDA) governing clinical, laboratory, and manufacturing practices. In addition, most federally supported clinical research is subject to regulations established by the Department of Health and Human Services for the protection of human subjects.¹⁰ These regulations, originally promulgated in 1981, established a system based primarily on review boards and informed-consent procedures to ensure that the interests, rights, and safety of study participants were protected.

Two years ago, in response to the exponential growth in clinical investigation, as well as reports of deficiencies in the review, oversight, and conduct of trials, the Department of Health and Human Services reconstituted the Office for Protection from Research Risks as the Office for Human Research Protections. This new office is responsible for leading efforts to improve the system of oversight and enforcing the department's regulations. This office reports to the assistant secretary for health and is housed in the Office of the Secretary, ensuring its ability to function independently of but in collaboration with the National Institutes of Health, the FDA, and the Centers for Disease Control and Prevention. Since its inception, the Office for Human Research Protections has embarked on a major reorganization effort that calls on institutions, review boards, and investigators to join together in order to protect study subjects, ensure the integrity of clinical research, and strengthen public confidence in it. The office's programs of education, support, quality improvement, and surveillance are well under way, as are institutional efforts to strengthen their programs. Testimony by the General Accounting Office¹¹ and the articles by Christian et al. and Steinbrook substantiate these efforts. The Office for Human Research Protections has commissioned a study by the Institute of Medicine to review the progress of these efforts, and the results, which should be available in the fall, will warrant close attention as we plan for the future.

Over the years, the IRB has served as a *sine qua non* in the system of checks and balances for the protection of research subjects. However, as noted in this issue of the *Journal* and elsewhere, the increasing number and complexity of protocols are taxing the capability of local IRBs. Modifications of the traditional IRB system (e.g., private IRBs that work under contract and systems of accreditation) have been introduced

to help relieve the burden; in my opinion, other, more innovative models also merit consideration.

Christian et al. describe a pilot program developed by the National Cancer Institute in cooperation with the Office for Human Research Protections. Under this program, a central IRB provides an expert review of protocols for multicenter phase 3 trials. These reviews are communicated to the local IRBs, with a clearly delineated delegation of responsibilities that facilitates the local review and allows for individualization of protocols and informed-consent documents according to local considerations.⁷ Such a system should promote performance and increase access even for patients far from the centers of excellence. On the basis of its first year of operation, the pilot program appears to be working. Although follow-up data are limited, the concept of a central review board for multicenter protocols seems viable and warrants broader application.

Before victory can be declared, however, certain questions must be addressed. Somewhat worrisome is the statement by Christian et al. that the local investigators may not thoroughly understand "the rationale for a study, its design, or other issues that IRBs often address."⁷ How can that be? The local investigator should have a thorough understanding of the trial's objectives in order to assess the potential benefits as well as all potential risks. This knowledge is essential for the process of informed consent that must precede enrollment. Regardless of the type of review board (central, local, or contract), it does not have a direct responsibility to the patient. That belongs to the local primary investigator who enrolls patients. The IRB cannot be viewed as a substitute or surrogate for a responsible, well-trained, caring investigator. No matter how much we improve our system of checks and balances, the primary responsibility for full and thoughtful disclosure, enrollment without coercion, monitoring of the conduct of a trial, reporting of adverse events, and confidentiality must remain with the local primary investigator. This approach provides the essential basis for trust.

By and large, clinical research has expanded responsibly. Nonetheless, in his article, Steinbrook describes the deaths of healthy volunteers.⁹ These events occurred in 1996 and 2001, before many of the advances described in this issue. These deaths and several others, as well as the temporary suspension of clinical research at a number of medical centers, have been reported widely by the media and in major journals. Certainly, as compared with the numbers of patients studied, these deaths represent rare, albeit grave, events. Nonetheless, we must ask what we can learn from these data.

We will never be able to determine the exact incidence of adverse events and can therefore only spec-

ulate about the demographic aspects of errors in clinical trials. In reviewing the recent suspensions of federally supported research, should we be concerned that many of them occurred at medical centers of excellence where large numbers of clinical studies are performed?⁹ Is this a function of improved detection and reporting of adverse events or of the sheer volume of research performed at these centers? Proximity to centers of excellence should count for something in our reasoning. Can overwork undermine even the best systems? The rapid corrective actions described in both of Steinbrook's reports are laudable, but we should be prepared to look beyond the obvious. We must continue to be concerned that serious errors occur at all at major institutions. Have even the most productive and experienced clinical researchers spread themselves too thin? Why should service on IRBs be considered onerous? Perhaps the privilege of conducting clinical research should carry with it the responsibility to serve on the IRB. This is the forum for discussing and advancing clinical science; it provides an opportunity for teaching junior faculty members. Clinical research is analogous to an experiment in the laboratory, requiring attention to materials and methods, as well as design, analysis, and interpretation.

The initiatives described by Christian et al. and by Steinbrook are sound and are gaining acceptance, but even as we proceed with these improvements, we must not lose sight of our first priority. The subjects who volunteer for clinical trials are the true heroes of modern clinical research. It is the responsibility of our

profession to serve these persons to the best of our ability. Without their trust, the advancement of both clinical science and medical practice will falter.

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REFERENCES

1. Recruiting human subjects: pressure in industry-sponsored clinical research. Washington, D.C.: Department of Health and Human Services, Office of Inspector General, June 2000. (DHHS contract no. OEI-01-97-00195.)
2. Institutional review boards: a time for reform. Washington, D.C.: Department of Health and Human Services, Office of Inspector General, June 1998. (DHHS contract no. OEI-01-97-00193.)
3. Ethical and policy issues in research involving human participants. Vol. 1. Bethesda, Md.: National Bioethics Advisory Commission, August 2001.
4. Monitoring adherence to the NIH policy on the inclusion of women and minorities as subjects in clinical research: comprehensive report (FY 1997 and FY 1998 tracking data). Bethesda, Md.: National Institutes of Health, Office of Research on Women's Health, September 2000.
5. PAREXEL's pharmaceutical R&D statistical sourcebook 2000. Walham, Mass.: PAREXEL, 2000:77-8.
6. Snyderman R, Holmes EW. Oversight mechanisms for clinical research. *Science* 2000;287:595-7.
7. Christian MC, Goldberg JL, Killen J, et al. A central institutional review board for multi-institutional trials. *N Engl J Med* 2002;346:1405-8.
8. Steinbrook R. Protecting research subjects — the crisis at Johns Hopkins. *N Engl J Med* 2002;346:716-20.
9. *Idem*. Improving protection for research subjects. *N Engl J Med* 2002; 346:1425-30.
10. Protection of Human Subjects, 45 C.F.R. 46 (June 18, 1991).
11. Henrich J. Human subjects research: HHS takes step to strengthen protections, but concerns remain. Washington D.C.: General Accounting Office, May 23, 2001. (GAO-01-77ST.)

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