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# Advisory

June 2000

## HEALTH CARE

### Focus: Human Clinical Trials Clinical Trial Issues Suddenly Loom Large in Washington

Clinical trials, the process by which the safety and efficacy of new drugs and medical technology is tested, are becoming an issue of substantial federal concern. Long the province of the Food and Drug Administration (FDA) and local institutional review boards (IRBs), clinical trial oversight is now an issue for Congress and senior officials of the Department of Health and Human Services (HHS) as well. HHS earlier this month announced the creation of a new Office for Human Research Protection at the Secretary level to lead efforts in protecting human subjects. HHS said it will also create a new National Human Research Protections Advisory Committee.

Even the White House has turned its attention to clinical trials. In order to encourage a more representative patient population in clinical trials, President Clinton has ordered HHS to pay for medical care provided to a Medicare beneficiary participating in a clinical trial. President Clinton has also announced that he will ask Congress to give FDA the power to levy civil money penalties for infractions of human research subject protection rules. In a June 7 executive order, the President directed HHS to begin immediately providing Medicare coverage for beneficiaries enrolled in clinical trials. Despite the fact that seniors represent the largest sector affected by many of the diseases under study, only one percent of Medicare beneficiaries currently participate in clinical trials, thus potentially skewing the results. According to the White House, one of the reasons seniors are reluctant to participate in clinical trials is the uncertainty about whether or not Medicare will pay for the care associated with participation in a clinical trial. By authorizing Medicare coverage for medical care associated with clinical trials, President Clinton hopes to increase the number of American seniors who elect to participate in clinical trials.

Despite this new encouragement to seniors to participate in clinical trials, the flurry of federal activities may mean that recruiting volunteers for clinical trials will become more difficult and more carefully monitored. Any substantial changes may slow the already ponderous new drug development process.

The executive order builds upon the 1999 recommendations by the Institute of Medicine, which concluded that Medicare should explicitly

cover routine patient care costs for clinical trial participants. Specifically, the order directs HHS to:

- revise Medicare program guidance to explicitly authorize payment for routine patient care costs and costs due to complications associated with clinical trials;
- launch activities to increase beneficiary awareness of the new coverage option such as educating beneficiaries and providers about this policy change through developing a brochure, adding relevant information to future Medicare handbooks and posting information about clinical trials on the HHS websites;
- establish a system to track clinical trial spending to which Medicare contributes;
- ensure that information gained from important clinical trials is appropriately used to assist in making decisions about Medicare coverage. Specifically, the Health Care Financing Administration (HCFA) and the National Institutes of Health (NIH) are directed to work with researchers to structure clinical trials that may have significant implications for the Medicare program so that these trials produce information that will assist in making Medicare coverage decisions; and
- report back to the President within ninety days on additional actions to promote research on issues of importance to the Medicare population, including providing additional financial support for monitoring and evaluation, device implantation and other non-covered costs; increasing participation of seniors in clinical trials and developing a registry of all clinical trials receiving Medicare reimbursement.

HHS estimates that the cost of covering routine patient care and medical complications associated with clinical trials will be about \$350 million annually. Researchers are hopeful that this new initiative will assist them in recruiting older participants into clinical trials.

How clinical trial participants are recruited in industry-sponsored trials and how FDA oversees their participation is the subject of three new reports by the Office of Inspector General (OIG).

### OIG Faults Recruiting Process

In *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research* and *Recruiting Human Subjects: Sample Guidelines for Practice*, the OIG notes that there have been several recent changes in the environment in which clinical trials take place which impact the recruitment of human subjects. First, there is increased pressure for expedited enrollment into clinical trials. This is due, in part, to the rapid rise in the cost of developing drugs which is forcing sponsors to speed up the drug development process. Second, because of the increase in the number of drugs being developed, as well as the increased complexity of the trials, there is a growing need for larger numbers of subjects to fill clinical trials. Third, sponsors want to utilize only research sites that operate efficiently, which has led to a shift from conducting trials in academic settings to conducting them in private practice settings.

As a result of these changes, sponsors and investigators use a variety of strategies to recruit potential subjects. The report identifies four broad categories of strategies, including the offering of incentives, the targeting of a physician's own patients, the seeking of additional patient bases and the advertising and promoting of clinical trials. The OIG expressed three major

concerns about the effect these strategies have on the recruitment process:

- These recruitment practices may contribute to the erosion of informed consent. The OIG is concerned that information is not being presented in a manner that facilitates the subjects' true understanding of the risks and benefits of a particular trial. Additionally, there is concern about the effect the dual role physician-investigators may have on the voluntariness of the consent, given that patients often place a lot of trust in their treating physician and may be reluctant to deny participation in a trial recommended by their treating physician.
- The OIG is concerned that in an effort to expedite the recruitment process, sponsors and investigators may compromise patient confidentiality. Given the almost commonplace use of computers to maintain patient databases, it is easy to search medical records to identify eligible subjects. Not all patients sign informed consents authorizing third-party access to their medical records, or at least not for the purpose of being identified for a clinical trial. These patients are often unaware that people other than their physicians are reviewing their records and may contact them about participating in clinical trials.
- The OIG is concerned that the pressure to enroll participants quickly may lead investigators to enroll people who are ineligible. Given the current competitive environment, it is feared that some investigators may enroll participants to meet quotas and satisfy sponsors regardless of whether the subjects are clearly eligible. These types of enrollment practices raise major concerns about safety and data validity.

Despite the concerns about recruitment practices, there is currently minimal oversight of trial recruitment and the oversight that exists is generally unresponsive to the concerns enumerated, according to the OIG. IRBs do not review many of the troubling practices because they do not believe that they have the authority to conduct such review. Additionally, the OIG believes there is little guidance for IRBs, even if they did review recruitment practices. Sponsors also do not pay much attention to how subjects are recruited for their trials and HHS, in its inspections of IRBs and investigators, currently does not pay much attention to recruitment practices.

As a result of these findings, the OIG makes four recommendations jointly to FDA, NIH and the Assistant Secretary for Health (ASH). First, it recommends that FDA and NIH provide guidance (i) clarifying that IRBs do have the authority to review recruitment practices and (ii) suggesting how IRBs should exercise this authority. Second, it recommends that FDA, NIH and ASH facilitate the development of guidelines for all parties on appropriate recruiting practices. There should be adequate representation in the guideline development process from sponsors, industry groups, investigators, IRB representatives, patient advocates and ethicists. Third, it recommends that IRBs and investigators be adequately educated about human-subject protections. Education should be required for investigators before conducting human-subject research. IRBs should have a training program for board members. Additionally, there should be more extensive representation of nonscientific and noninstitutional members on IRBs. Fourth, it recommends that federal oversight of IRBs be strengthened. This could be accomplished by requiring all IRBs to register with, and regularly report to, the federal government. Further, FDA

on-site inspection process could be revised to address the concerns expressed in the report.

While the report on *Pressures in Industry-Sponsored Clinical Research* addresses in general terms certain concerns of the OIG about the recruitment process and concludes that the current FDA and NIH guidelines do not address these concerns, the companion report, *Sample Guidelines for Practice*, focuses on guidance that is currently available from IRBs, medical associations and Canada on the three main concerns noted above—recruitment incentives, the dual investigator-physician role and the confidentiality of medical records. This report, as well as the others discussed in this Advisory, are available at [www.hhs.gov/oig/oei/whatsnew.html](http://www.hhs.gov/oig/oei/whatsnew.html).

### FDA Oversight Found Wanting

Can FDA protect the rights and welfare of human subjects in clinical research? The OIG in a report released on June 12, 2000, responded to that question by saying “Only retrospectively.” In *FDA Oversight of Clinical Investigators*, the OIG examined FDA’s selection of clinical investigators for inspection and FDA’s discipline of those clinical investigators found in violation of FDA’s regulations. The OIG found that while FDA may successfully ensure the quality and integrity of data submitted to the agency by clinical investigators involved in clinical trials, FDA does not have the capacity nor is its oversight program properly structured to protect the rights and welfare of the human subjects.

The primary problem identified by the OIG is that FDA’s bioresearch monitoring program inspects clinical investigators involved in clinical trials after the clinical work is complete. While such a monitoring program may assist in ensuring quality and integrity of data, it has no chance of being able to protect the human subjects involved in the clinical trial. The current FDA

system is not intended to provide day-to-day oversight of clinical trials; rather, it provides a retrospective review. Thus, data integrity concerns, more than human subject protection, drive FDA’s oversight of clinical investigators.

Adding to the weaknesses of FDA’s bioresearch monitoring program, according to the OIG, is that it lacks clear and specific guidelines. There is no required review of complaints or clinical investigator inspection histories as part of the clinical investigator selection process. FDA’s monitoring staff do not receive much, if any, formal training concerning how to select clinical investigators for inspection, or how to assess what action is appropriate when violations are detected. For example, inspection decisions are based on site size, inspection history and data issues. This raises the concern that clinical investigators with small numbers of subjects will never get visited. Furthermore, there are no written guidelines defining key standards for violations. The OIG reports that there are varying ideas concerning what constitutes an “official action indicated” classification. There is a general consensus among FDA staff that while there is no formalized definition of “repeated or deliberate” violations, “You know it when you see it.” Finally, FDA does not have agency-wide program measures or goals for the bioresearch monitoring program.

The OIG’s recommendations focus on improving FDA’s oversight of clinical investigators. To improve the bioresearch monitoring program, the OIG recommends that FDA define goals for the bioresearch monitoring program and develop criteria to determine whether the program is achieving those goals. FDA should also recognize the limitations of the current system’s ability to protect human subjects during clinical trials, as currently, any human subject violations identified are found

too late to protect the human subjects involved. Finally, the OIG recommends that FDA develop internal guidance on the thresholds that violations must meet to justify disqualifying a clinical investigator from receiving investigational products. Having a written framework would provide structure for FDA reviewers.

The OIG recognizes that FDA attempts to protect human subjects and the general public through retro-

spective review of clinical investigators, research sponsors and institutional review boards. The OIG concedes that FDA is not responsible for providing patient care and is not currently equipped to monitor studies during the research process.

Last month, the Clinton Administration announced that it would seek legislation authorizing FDA to levy fines for violation of human research subject protection requirements. FDA currently has

enforcement tools that one official characterized as a light hammer and a sledgehammer, a warning letter or shutting down the clinical trial. The use of civil money penalties is considered an “intermediate” sanction. It is not clear what sort of reception proposed legislation would receive on Capitol Hill.

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