

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

Recruiting Human Subjects

Pressures in Industry-Sponsored Clinical Research



**JUNE GIBBS BROWN
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EXECUTIVE SUMMARY

PURPOSE

To evaluate the Department of Health and Human Services' (HHS) oversight of sponsor and investigator efforts to recruit human subjects for industry-sponsored clinical trials.

BACKGROUND

Protecting Human Subjects

In a June 1998 report, *Institutional Review Boards: A Time for Reform*, (OEI-01-97-00193), we identified weaknesses in the system intended to protect human subjects who participate in clinical trials. Since the release of our series of reports on institutional review boards (IRBs), both the Office for Protection from Research Risks (OPRR) in the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) — the two bodies responsible for human-subject protections within the Department — have taken action against many research institutions, reflecting the strong Federal stance we called for in the recommendations of our report. OPRR has cited a number of research institutions for non-compliance with Federal regulations and temporarily suspended ongoing research at seven of these institutions. More recently, FDA terminated all gene therapy research after finding serious deficiencies in human-subject protections at another center. These collective actions support and respond to the findings in our report concerning the safety net for protecting human subjects.

This Inquiry

In this report, we follow up our prior report by focusing on one aspect of the clinical research process, the recruitment of subjects into industry-sponsored clinical trials. We have chosen to focus on industry-sponsored trials because in recent years the clinical research environment has become more commercialized and competitive, as industry sponsors have assumed a more prominent role in the search for new drugs. In this changing environment, with significant increases in the number and complexity of clinical trials, the quest to find human subjects has intensified. Sponsors and investigators are facing increasing difficulty finding enough subjects in a timely manner to bring drugs to market within their desired time-frame.

In this report and our companion report, *Recruiting Human Subjects: Sample Guidelines for Practice* (OEI-01-97-00196), we focus on the recruitment practices used in industry-sponsored clinical trials for investigational drugs. We explain the practices, identify major concerns about them, and address the extent and type of oversight undertaken by IRBs and, within HHS, by the FDA and NIH.

Our inquiry is based on a survey of a random sample of IRBs; a review of FDA's database of IRBs and investigators involved in investigational new drug research; a review of FDA's IRB and clinical investigator inspection process, including participation in two FDA inspections; six site visits to research sites; reviews of existing Federal guidelines; interviews with numerous parties involved in each step of the recruitment process; and an extensive literature review.

FINDINGS

In this report, we focus on human subject recruitment for two main reasons. One is that recruitment is a vital first step in the consent process, one that must not in any way be coercive or misleading to the potential subjects. The second is that recent investigations and complaints reveal disturbing recruitment practices: a study in which patients were recontacted numerous times in an effort to persuade them to enroll; a nursing home resident who was forced to participate in a study or leave the home; and a subject, later found to be ineligible, who died after participating in a trial.

Sponsors and investigators use four main strategies to recruit human subjects and encourage timely recruitment.

- ▶ Sponsors offer financial and other incentives to investigators to boost enrollment.
- ▶ Investigators target their own patients as potential subjects.
- ▶ Investigators seek additional subjects from other sources such as physician referrals and disease registries.
- ▶ Sponsors and investigators advertise and promote their studies.

IRB officials and others closely involved with clinical research express many concerns about current recruitment practices.

Erosion of Informed Consent. The most fundamental concern is that the consent process may be undermined when, under pressure to recruit quickly, for example, investigators misrepresent the true nature of the research or when patients are influenced to participate in research due to their trust in their doctor.

Compromise of Confidentiality. Many people raised concerns about someone other than the patient's physician searching medical records and then contacting a patient about participation. They also raised concerns about investigators' use of other records such as disease registries, school records, or mailing lists.

Enrollment of Ineligible Subjects. Research observers fear some investigators may be led to enroll subjects that are ineligible, or of questionable eligibility, in order to meet quotas and satisfy sponsors.

Oversight of the recruitment of human subjects is minimal and largely unresponsive to emerging concerns.

- ▶ IRBs are not reviewing many of the recruitment practices that they and others find most troubling.
- ▶ IRBs' limited review of recruitment practices is in part due to their perceived lack of authority to review certain practices.
- ▶ HHS provides little guidance to IRBs on acceptable recruitment practices. In contrast, some professional medical associations provide strong guidance on selected issues.
- ▶ In their own oversight of research sites, sponsors pay minimal attention to how human subjects are recruited.
- ▶ Nor does HHS pay much attention to recruitment practices in its inspections of IRBs and investigators.

RECOMMENDATIONS

The critical challenge is to ensure essential human-subject protections without unnecessarily slowing the pace of research and discovery. With that objective, below we offer recommendations jointly to the FDA, NIH, and the Assistant Secretary of Health (ASH). We include ASH because the Secretary of HHS recently announced that OPRR will soon move from NIH to the Assistant Secretary's office.

The first two recommendations specifically relate to the oversight of human-subject recruitment. The last two relate to the oversight of human-subject protections more generally, but are integral to the oversight of recruitment. Although our methodology focused on drug research, we expect that our findings and recommendations would also apply to other types of human-subjects research, such as devices and biologics.

1. Provide IRBs with direction regarding oversight of recruitment practices

Clarify that IRBs have the authority to review recruitment practices. FDA and OPRR should disseminate guidance explicitly stating this authority based on IRBs' established authority to ensure informed consent and review anything related to human-subject protections.

Provide guidance to IRBs on how to exercise this authority. FDA and OPRR should suggest recruitment questions that boards should address in their protocol reviews and should foster discussion about these issues.

2. Facilitate the development of guidelines for all parties on appropriate recruiting practices

A clearer determination of *appropriate* recruiting practices would be helpful for all parties — sponsors, investigators, and IRBs. It is essential that this determination be made cooperatively with industry and the research community. As part of their deliberations, these parties could explore such questions as:

- ▶ Is it acceptable for sponsors to offer bonuses to investigators for successfully recruiting subjects?
- ▶ Should physicians be allowed to receive fees for referring their patients as potential subjects for a clinical trial?
- ▶ Should the financial arrangements between sponsors and investigators be disclosed to potential subjects?
- ▶ Does searching medical records for potential subjects constitute a breach of confidentiality?

An examination of the feasibility and effectiveness of institutional policies currently in place could also provide useful information for those considering an expansion of current Federal guidance.

3. Ensure that IRBs and investigators are adequately educated about human-subject protections

- ▶ Require investigator education as a prerequisite for conducting research under FDA authority or before receiving funds under the Public Health Service Act.
- ▶ Require that IRBs have a training program for members.
- ▶ Require more extensive representation on IRBs of nonscientific and noninstitutional members. Such members can help sensitize IRBs to patient concerns about recruitment practices.

4. Strengthen Federal oversight of IRBs

- ▶ Require that all IRBs register with the Federal government and regularly report basic descriptive information.
- ▶ Revamp the FDA on-site inspection process.

COMMENTS ON THE DRAFT REPORT

We received comments on our two draft reports from HHS. We also solicited and received comments from the following external organizations: Public Citizen’s Health Research Group, Pharmaceutical Research and Manufacturers of America, Applied Research Ethics National Association in conjunction with Public Responsibility in Medicine & Research, and the Consortium of Independent Review Boards. We did make a number of changes in the final reports, many technical in nature, that respond to their comments. Below we summarize the major comments and offer our response to HHS and, collectively, to the external parties.

HHS Comments

HHS shared our concern about some current recruitment practices and agreed that such concerns could be minimized if it were to provide IRBs with guidance on appropriate practice. It agreed to work with professional societies and others to develop this guidance. Although HHS disagreed with our assertion that current guidance documents from FDA and NIH are unclear about IRB’s authority to review certain recruitment practices, it indicated that the new office in the Office of the Secretary would revisit this guidance and augment it as necessary. HHS indicated its commitment to establishing educational requirement for investigators, IRBs, and IRB staff and that efforts are underway within FDA to register IRBs.

We are pleased that HHS has made such a significant commitment to establishing education requirements. We are also pleased that HHS has agreed to work with outside parties in developing consensus about appropriate recruitment practices. We encourage the Department to continue its current efforts to register IRBs. Although we agree that NIH and FDA already have guidance documents indicating that IRBs have authority to review recruitment practices, we found that many IRBs are uncertain of this authority, suggesting that clearer guidance is needed.

External Parties’ Comments

Overall, external parties echoed the concerns we raised about some current practices for recruiting subjects into clinical trials and agreed that steps should be taken to identify, at

a national level, appropriate recruitment practices. External parties' comments to our report raised a few common concerns. One concern was that our recommendations would prompt Federal bodies to dictate appropriate recruiting practices without input from outside groups. Another was that already overburdened IRBs would be asked to add to their duties by suggesting that they review recruitment practices. Finally, there were several questions and concerns about our methodology, including the scope of the study and the evidence upon which our findings are based.

We clarified some of the language we used in our draft report to elucidate our belief that guidelines for appropriate recruiting practices should emerge from a dialog among all of the key parties involved in clinical research, including IRBs, sponsors, investigators, as well as Federal bodies. We believe that our recommendation that HHS clarify IRBs' authority for reviewing recruiting practices would not add significantly to the boards' workload. Many IRBs already review recruitment practices; national guidelines on appropriate practices would reduce the time now required for IRBs to debate the future use of such practices. Regarding our methodology, we sought to document current recruitment practices in industry-sponsored research and any concerns raised by these practices; we did not judge the appropriateness of any of these practices, nor did we differentiate these practices and concerns by funding source. Our analysis was primarily qualitative, based on interviews and observations, due to the nature of the study topic.

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INTRODUCTION

PURPOSE

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BACKGROUND

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Recruitment as a Human-Subject Protection Issue

In this report, we follow up our prior report by focusing on one aspect of the clinical research process, the recruitment of subjects into clinical trials. Recruitment warrants special attention because it marks the first step in the informed consent process and, thus, must not be coercive or misleading. Second, as we found in a prior report, oversight bodies almost never witness the actual consent process.¹ The review of some recruitment methods, particularly advertisements, provides additional opportunity for oversight bodies to monitor the actual content of the consent process. Third, little is known outside the research community about the ways in which subjects are recruited. An understanding of these practices is important in order to target effective oversight.

Several recent Federal investigations and complaints raise concerns associated with recruitment: a study in which patients were recontacted numerous times in an effort to persuade them to enroll; a nursing home resident who was forced to participate in a study or leave the home; and a subject, later found to be ineligible, who died after participating in a trial.

Oversight of Human-Subject Protections

Two agencies within HHS are responsible for protecting the rights and welfare of human subjects participating in clinical research: the FDA and NIH. As part of its oversight of clinical trials, FDA oversees research on products it regulates. Currently, NIH, through its Office for Protection from Research Risks (OPRR), oversees research funded by HHS. Both NIH and FDA delegate most of the direct authority for reviewing human-subjects research to institutional review boards. These boards, known as IRBs, are charged with reviewing research protocols and ensuring that adequate human-subject protections are in place.

This Inquiry

This report focuses on industry-sponsored research. We are focusing on this research because the financial incentives to create effective and competitive drugs profitably are more pronounced in industry-sponsored research than in research funded by the government. We are aware that government-funded research is not immune to these and other pressures; therefore, we may follow up later by focusing on recruitment in government-sponsored trials.

It is important to note that the thrust of our information gathering for this report was to gain a better understanding of the concerns associated with recruiting practices. We recognize that there are many investigators who are conscientious in their recruiting of subjects and who seek to better understand how to educate potential subjects about clinical research and what it entails.

Because of the potential for overlapping jurisdiction, we chose to review both FDA's and OPRR's oversight processes. Our focus on industry-sponsored clinical research would normally lead to an examination of FDA's oversight of subject recruitment. However, OPRR's oversight mechanism, the assurance document, is applied at many institutions to all research conducted at that institution regardless of funding source.

We also focus on biomedical research, specifically drug-development research, rather than psychological, sociological, or other types of research that do not result in a marketable product. Furthermore, we concentrate on drug trials rather than medical device trials, because drug trials represent the majority of ongoing research. There are trials involving certain diseases for which sponsors have no difficulty finding a sufficient number of subjects; in these cases, there is a reverse struggle of trying to meet patients' demands to be subjects in a limited number of clinical trials. We will not be addressing this "limited supply" issue that occurs in a minority of clinical trials.

Methodology

We surveyed a random sample of IRBs; reviewed FDA and OPRR processes; analyzed FDA's Center for Drug Evaluation and Research database of IRBs and investigators involved in Investigational New Drug research; conducted six in-depth site visits to both academic and independent research sites; reviewed FDA's inspection process, including accompanying FDA inspectors on two inspections; reviewed existing guidelines; interviewed numerous parties involved in each step of the clinical research process; and conducted a thorough literature review. A more detailed description of our methodology can be found in appendix A.

We conducted this inspection in accordance with the *Quality of Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

The Main Players in Clinical Trials

Clinical trials for new drugs are complex and require the engagement of many different entities. In recent years, the number of these entities and their agents has proliferated. Below, we attempt to describe the roles of and interactions among these players.

Sponsors

Pharmaceutical companies, which we refer to as *sponsors* in this report, are responsible for proving the safety and efficacy of investigational drugs, through clinical trials, to the FDA. Sponsors are also responsible for conducting on-site oversight of their trials. This oversight is carried out by *monitors*. Traditionally, sponsors have not only conducted basic drug research and development, but have conducted the clinical trials needed to gain FDA approval of the drug. Recently, in an attempt to reduce their research and development costs and to streamline processes, sponsors have started outsourcing many aspects of clinical trials to other entities. Sponsors often delegate a variety of specialized functions, such as the organization and management of clinical trials, to *contract research organizations* (CROs) which sometimes, in turn, outsource to other specialized entities. *Patient recruitment firms*, public relation firms whose sole mission is recruiting human subjects, have emerged in recent years in response to sponsors' and CROs' desire for speedy recruitment of subjects. For the purposes of this report, the term "sponsors" refers to sponsors and their agents, including monitors, CROs, and patient recruitment firms.

Investigators and Research Sites

Sponsors depend upon physicians, called *clinical investigators*, to actually conduct clinical trials. Investigators often rely on their staff to handle the administrative and sometimes much of the clinical work associated with clinical trials. Often, investigators will have a point person, or *study coordinator*, a practitioner (generally a nurse) whose primary responsibility is to facilitate the conduct of clinical trials. Coordinators may be involved in recruiting and consenting subjects, as well as maintaining the data for the trial. In this report, the term "investigator" refers to all practitioners involved in conducting clinical trials, including study coordinators, sub-investigators and others.

Investigators conduct trials in a variety of different settings. Traditionally, they have conducted clinical trials primarily in university hospitals, or *academic medical centers* (AMCs). Increasingly, research occurs in physicians' private practices or in *dedicated research sites*, sites exclusively used for research. Some investigators and/or sites have tried to accommodate sponsors' desire for efficient, streamlined trial conduct by forming site networks, sometimes referred to as *site management organizations* (SMOs).

Human Subjects

The final, and most critical, players in a clinical trial are the human subjects themselves. Subjects may be recruited by an assortment of agents and/or entities: sponsors, CROs, clinical investigators, research coordinators, and patient recruitment firms. In general, sponsors use healthy subjects to test the safety of a drug in first-in-human trials. They use subjects with the condition they are targeting to test the efficacy of a drug in later-stage trials.

A Changing Clinical Trials Environment

In a highly competitive environment, sponsors and investigators face growing difficulty finding subjects and finding them quickly

The clinical research environment is evolving rapidly, with many of the changes creating significant competition for all players in the clinical trials arena. There has always been, and will continue to be, a public interest in bringing useful, potentially life-saving drugs to market quickly. However, recent changes in the research environment are causing sponsors to vie more aggressively to be the first to bring their product to market and are causing sites and investigators to compete more intensely for research contracts. Three of these changes particularly impact human-subject recruitment.

Change	Explanation
<p>Increased Pressure for Quick Turnaround Times</p>	<p>Higher drug development costs. The cost of developing new drugs is growing rapidly. In the past 20 years, the average cost of developing a drug has grown almost 10-fold from \$50 million in the 1970s to \$400-500 million in the 1990s.² Pharmaceutical companies claim that they need to constantly increase the percentage of their expenditures allocated to research and development in order to remain competitive within the industry.³</p> <p>Increasing industry investment in research and development. Between 1998 and 1999, sponsors increased their world-wide research and development investments by 14 percent and have nearly tripled this investment between 1990 and 1999.⁴ As developing drugs becomes more costly, sponsors are increasingly anxious to get their products to market quickly in order to recoup these initial outlays. Thus, they are trying to speed up the drug development process, of which subject recruitment is part.</p>
<p>Intensified Search for Human Subjects</p>	<p>More drugs in development. Pharmaceutical companies are developing more drugs now than ever before. In 1995, there were 2,585 drugs in pre-clinical testing; by 1998, that number had risen to 3,278.⁵</p> <p>More subjects needed for each trial. In addition, clinical trials are becoming more complex and are requiring far more subjects per trial than before.⁶ An average of 4,237 subjects were used in New Drug Applications from 1994 to 1995, compared with an average of 1,321 subjects from 1981 to 1984.⁷ Sponsors are struggling to meet this increasing need for human subjects.</p>
<p>Quest for More Efficient Research Sites</p>	<p>Commercial research shifting to private settings. Pharmaceutical companies are seeking the quickest, most efficient settings to conduct their clinical trials. Increasingly, they are shifting out of the academic medical centers (AMCs). Approximately 50 percent of industry-sponsored trials are conducted in AMCs now, compared with 80 percent 5 years ago.⁸</p> <p>Growth of private-practice investigators. Industry-sponsored trials are increasingly leaving AMCs and flowing into private practice settings. The number of private-practice based investigators increased from 3,513 in 1990 to 11,588 in 1995.⁹ This growth is part of a larger influx of investigators into the clinical trials arena. The number of new investigators increased approximately 22% annually between 1992 and 1996.¹⁰</p>

Quick Turnaround Times

Many of the investigators, monitors, and other players in the clinical trial arena whom we interviewed noted a trend towards increasingly tight enrollment deadlines. As one investigator stated, “In the past 10 years there has been way more pressure to recruit; studies that used to take 1½ years to enroll [are] now [supposed to] take 3 months.” A typical explanation we heard of these “unrealistic” deadlines was that, increasingly, business people rather than clinicians are making decisions about enrollment goals and deadlines. Asked what sponsors are looking for from sites, one investigator responded, “Number one—rapid enrollment. Number two—rapid enrollment. Number three—rapid enrollment.” Virtually every investigator mentioned that a site’s ability to recruit quickly is one of the main qualities sponsors attempt to assess before contracting with a site, a belief that is supported by the literature.¹¹

Shorter enrollment deadlines reflect pharmaceutical companies’ struggle to remain profitable in a business that requires enormous investments of time, money, and risk before a product can reach the market. The clock for a drug patent starts running when the patent application is filed, which is prior to the clinical testing of the drug. Thus, sponsors wish to shorten the testing phase, as they are anxious to recoup research and development costs of their drugs before a generic or therapeutically similar drug appears on the market. Recruitment, a major bottleneck in the flow of drugs through the development pipeline, is one of the main aspects of clinical testing that sponsors are trying to shorten.¹² Although pharmaceutical companies are setting shorter deadlines in hopes of hastening the recruitment process, most trials fail to meet these deadlines.¹³

Sponsors and their agents constantly remind sites of the need to expedite recruitment. Sites report numerous phone calls from sponsors, informing them of how their enrollment statistics compare with those of other sites in the trial. One investigator, who was the top recruiter on a trial, told us that the sponsor called every week to urge her to keep enrolling so that she did not lose her “#1” status. Other sites report receiving newsletters with charts comparing enrollment at their site to others, faxes goading them to speed recruitment, and other reminders comparing their enrollment with that of other sites.

Intensified Search for Subjects

Not only do sponsors want rapid enrollment of subjects, but they also need increasing *numbers* of subjects to fill more and larger trials. More and more drugs are being developed as advances in biomedicine and genetics enable scientists to further understand disease mechanisms, and as pharmaceutical companies increase productivity to be competitive.¹⁴ These trials need to be filled by an ever-growing number of subjects.

In addition, trials need to be filled with subjects that meet particular eligibility criteria. Defining appropriate eligibility criteria is an essential part of designing a trial, but these criteria also have broad implications for recruiting subjects. Virtually everyone we

interviewed cited overly restrictive eligibility criteria as one of the biggest barriers to enrollment. “They [sponsors] are asking us to find subjects that simply don’t exist” was a complaint we frequently heard in one form or another.¹⁵ Sponsor representatives also seemed well aware of this problem. The main explanation for these tighter eligibility criteria, given by both sponsors and investigators, is that sponsors need to prove the efficacy of their drug to increasing numbers of “customers,” including FDA reviewers, foreign regulators, clinicians, and the public. Particularly in the case of clinical trials for therapeutically similar drugs, even small improvements in efficacy can confer a tremendous marketing advantage for the experimental drug over the currently available, competing drug.¹⁶ Thus, sponsors design clinical trials to limit confounding factors. One investigator took this explanation further, claiming that sponsors “enrich trials with patients who are most likely to benefit.”

A particularly troublesome eligibility criterion cited by many investigators is the exclusion from a trial of potential subjects who are either currently on medication to treat their condition, or have been on medication in the past. Subjects that have never been on medications are known in the industry as “naive” subjects. Investigators mentioned that it is virtually impossible to find these “naive” subjects, particularly in some therapeutic areas for which medication is the standard of care, such as asthma or hormone replacement therapy. Only those lacking access to drugs, such as the uninsured or some foreign populations, would not be on medication for these conditions.

Many investigator and industry sources that we spoke to noted that sponsors are increasingly looking abroad for such subjects. In the past decade, there has been enormous growth in the number of new foreign investigators involved in trials testing drugs for FDA approval. According to our analysis of an FDA database, the number of new foreign investigators increased from 988 in the 1990-92 period to 5,380 in the 1996-98 period. Although sponsors’ search for “naive” subjects abroad has undoubtedly contributed to the increase in the use of foreign investigators in U.S.-based trials, other causes explain this proliferation of foreign investigators. Foreign research sites are often less costly to operate, may provide sponsors with access to populations with a high prevalence of the condition being studied, and, after testing, may facilitate launching the drug globally.¹⁷

Quest for Efficient Research Sites

“More, faster, and better”— we heard this phrase repeatedly from a variety of players in the clinical trials industry to describe sponsors’ desire for improved subject recruitment. Research sites are often competing with one another on the basis of their ability to recruit subjects.

Sponsors seek research sites that can test drugs most efficiently and have access to the most subjects. Increasingly, sponsors are finding academic medical centers, the traditional site of research, to be slow and cumbersome compared with private practices

or dedicated research sites.¹⁸ The representatives of academic centers that we spoke with felt that it was difficult to compete with investigators in other research settings in terms of both numbers and speed of subject enrollment. Private sites are able to begin enrollment sooner than academic centers because private sites generally use an independent IRB rather than the traditionally slower academic IRBs. Finally, private-practice doctors often have a much larger patient base to tap for recruiting certain subject groups than investigators in academic centers, which are tertiary care centers. One research nurse, who left research in an academic center to open her own dedicated research site, said that when she had conducted clinical trials in an academic center, she and her staff were always hustling to keep up with the private sites and, as a result, had a hard time convincing sponsors to contract with them.

As industry-sponsored research has migrated out of the academic centers, the number of new investigators conducting clinical trials has exploded. This proliferation of investigators is due, in part, to sponsors' increasing acceptance of non-academic investigators. The increase is also a response to a growing need for investigators, fueled by the growing numbers of clinical trials. Also, many investigators have turned to clinical trials to compensate for managed care-driven reductions in patient-care revenue.¹⁹

Many of the researchers we interviewed noted that the introduction of these new investigators into the clinical trials arena was exacerbating the competitive aspect of the clinical trials "business," both inside and outside of the academic centers. Sponsors seem to be capitalizing on the increase in the supply of investigators. In addition to cutting study budgets, we found that sponsors are using their market advantage to encourage investigators to accelerate enrollment.²⁰ First, before a contract is signed, sponsors will ask the investigator or site manager to estimate the numbers of subjects that the site can enroll. Sites are aware that if they do not give a high estimate, they probably will not be given the contract. Not surprisingly, sites often overestimate the number of subjects they expect to recruit, a frustration frequently reported by the sponsors and their agents with whom we spoke. Second, sponsors will often explicitly state when contracting with a research site that the site will be dropped if they do not enroll adequately. In this market-driven research environment, where one's ability to enroll adequate numbers quickly is crucial to one's competitiveness, poor enrollment on a trial could ruin a site's chance for future participation in trials.

FINDINGS

Sponsors and investigators use four main recruitment strategies to recruit human subjects and encourage timely recruitment

In response to the difficulties they face in recruiting subjects for clinical research, sponsors and investigators use myriad methods to identify, inform, and recruit subjects.²¹ We identified four broad recruiting strategies which encompass a number of specific methods. Below, we identify the four strategies, the corresponding methods, and a brief explanation of their implementation. We further describe them and offer examples in the following pages.

Recruitment Strategy	Examples of Methods	Brief Description
Offering Incentives	Financial Incentives	▶ offering an additional payment per subject enrolled above the study budget; seen most often as an enrollment deadline nears and additional subjects are still needed
	Nonfinancial Incentives	▶ items include office equipment, educational stipends, and authorship on journal articles presenting research results
	Competitive Enrollment	▶ organizing trials so sites in a multi-center trial compete to fill available subject slots on a first-come, first-serve basis
Targeting Own Patients	Referring Own Patients to Trial	▶ identifying eligible patients when they come in for appointments or through chart reviews
Seeking Additional Patient Bases	Referrals from Other Physicians	▶ sending information about ongoing research to other local physicians, asking for referrals, and occasionally offering fees to induce referrals
	Dissemination of Information to Relevant Groups	▶ distributing trial information to appropriate disease advocacy groups or student groups, perhaps by giving lectures or presentations to such groups
Advertising and Promotion	Media Ads	▶ describing the trial, including study requirements, eligibility criteria, and a contact for more information; can be found in newspapers, on radio, television, or on Internet sites
	Press Releases / News Segments	▶ compiling trial information in the form of a press release for airing on news programs or as a news article
	Special Events	▶ disseminating information in speaking engagements, such as local community organizations, health fairs, or medical screenings

Offering Incentives

The use of certain recruitment methods illustrates the transformation of clinical research into a traditional business model. Sponsors provide incentives, both financial and nonfinancial (see box), to investigators to encourage speedy enrollment and/or reward those that recruit certain numbers of subjects. Also, whereas before each site was allotted a certain number of subject slots, many trials now are conducted as “competitive enrollment.” Because sponsors pay sites per subject enrolled, competitive enrollment penalizes those sites with a slow start-up period and encourages aggressive recruiting.²²

“...The order on the author list will be determined by the number of patients enrolled, so that the center which enrolls the highest number of patients will obtain first authorship...”

From a sponsor-investigator contract

The use of financial enrollment bonuses appears to have increased somewhat in the past few years, despite evidence that such incentives are often ineffective.^{23,24} A coordinator we spoke with reinforced this notion when she told us her site “had gotten burned by enrollment bonuses in the past” because it enrolled all of its subjects before the bonus was offered. She told us, “we’ll think about that the next time around,” and possibly wait to enroll all of their subjects.

It is important to distinguish the financial incentives used to encourage timely recruitment from the sponsor payments to investigators for costs associated with conducting clinical research. Research costs vary significantly based on the requirements of the trial and can be very high when many expensive procedures are involved. When we refer to financial incentives for recruitment, we are referring to payments given to investigators purely to encourage speedy enrollment. Sponsors offer these incentives most often as an enrollment deadline nears or is passed.

The distinction between payment and enrollment incentives, however, can get blurred in practice. As sponsors continue to cut initial study budgets, many investigators that we spoke with reported that bonuses can help sites recoup the costs of conducting trials. These investigators often stated that they would rather have the initial study budgets accurately reflect the trials’ costs. One investigator discussed a study in which he was initially paid \$12,000 per subject enrolled. After other investigators in the trial complained to the sponsor of excessively tight budgets, the sponsor added a \$30,000 bonus once a site enrolled its first six subjects and, after these first six subjects were enrolled, the site would receive an additional \$6,000 per subject. The investigator, in describing this bonus scheme, emphasized that the sponsor had chosen to reimburse investigators by using bonuses to encourage recruitment rather than just revising the contract to reimburse investigators \$18,000 per subject enrolled.

Targeting Own Patients

For many investigators, their own patients are a vital source of subjects. Nearly all of the investigators we spoke with told us that they first tried to enroll any of their patients that were eligible. As an investigator at an academic center told us, he saw a direct correlation between his clinic time and his ability to recruit. When he reduced his clinic time to one half-day per week, his recruitment declined significantly; when he increased his time, his recruitment resumed accordingly. Similarly, investigators who lack certain types of patients often experience difficulties enrolling for those trials. For example, an academic physician we spoke with told us he had a hard time recruiting for one of his clinical trials because the trial focused on a common ailment. At the tertiary care center where he practiced, he rarely saw such common diseases which are easily treated by community physicians.

Patients are an important source of subjects in both academic and independent research settings. Even though many independent centers are free-standing entities, these sites contract with investigators who specialize in the condition under study, in large part because the investigators have potentially eligible subjects among their patients. The investigators will then refer their patients to the research site.

An advantage to using one's own patient base is the relative speed and ease with which investigators can reach these potential subjects. In fact, when asked what sponsors are looking for in placing a research study, both sponsor representatives and investigators told us that access to eligible patients is key. Sponsors seek out investigators and sites with large patient populations when looking to place trials.²⁵

Investigators recognize this and, in turn, have begun to advertise their large patient bases. Such advertisements are numerous and prominent, particularly on the Internet, as investigators reach out to sponsors to place a trial with them (see box).²⁶

Looking for Trials!

We are a large family practice office with 4 physicians and 3 Physician Assistants. We have two full time coordinators and a computerized patient data base of 40,000 patients....We are looking for Phase 2-Phase 4 trials as well as postmarketing studies. We can actively recruit patients for any study that can be conducted in the Family Practice setting.

**An Internet advertisement directed to sponsors
by a private practice seeking research
opportunities.**

Seeking Additional Patient Bases

When sponsors and investigators need more subjects, they target their search efforts to reach large groups of potentially eligible subjects, such as other physicians' patient bases or disease advocacy groups. Occasionally, investigators offer fees to encourage referrals from other physicians or nurses. For example, one coordinator told us that a site she had

formerly worked at offered \$75 to physicians or nurses for each subject referred. Another investigator told us about a local site that offered referring physicians a reimbursement of 10 percent more than Medicare reimburses for services that this physician provided as part of the trial.

The researchers we spoke with said that they rarely hear referral fees offered. This may be due, in part, to the fact that many investigators find referrals to be an unsuccessful method of identifying additional subjects.²⁷ The investigators who found referrals fruitless believed other physicians lack the time and the interest in research to approach their patients about participating. In addition, several academic physicians felt that community physicians were concerned that if they referred their patients to a trial, the academic investigators might take over all of the patients' care, thus "stealing" their patients.²⁸

Advocacy groups and student populations are another source of subjects. Advocacy groups often encourage researchers to develop new treatments for their disease. Many of these groups are eager to disseminate research information through their member networks and newsletters. Several investigators told us that they sometimes give presentations at advocacy meetings in which they try to mention their ongoing research protocols. For trials requiring healthy subjects, many sponsors and investigators reach out to student populations. Areas of high research activity are often located close to large universities.²⁹

Promotion and Advertising

Advertisements seeking human subjects are common. They can be found in newspapers, on the radio, the Internet, television, or as posters in, for example, public transportation or hospitals. Ads can be very expensive, especially in certain parts of the country. Because of this, many researchers are reluctant to use them unless absolutely necessary. Several researchers told us that ads are cost-effective only for studies in which the eligible population is large and widely dispersed (i.e., depression or heart disease) as opposed to rarer conditions such as cystic fibrosis.

Recently, sponsors and CROs have been helping sites recruit by initiating national recruitment campaigns for multi-site trials. The national efforts have spawned a new industry of patient recruitment firms and research marketing companies who are creating professional, elaborate marketing packages. Staff at the sites we spoke with report they are receiving more advertising from the sponsors at the start of the trial (including posters, fliers, and even prerecorded radio announcements for the local stations) than in years past. Many of these national advertisements include toll-free numbers. Call centers may provide operators who can screen respondents according to the trial's eligibility criteria and can schedule appointments at sites most convenient to callers. Or, the toll-free number may automatically transfer to a phone at the closest site.

The Internet is a fast-growing medium for advertising to potential subjects. As health care consumers make efforts to become more informed about their options, they are turning to the Internet as an important resource.³⁰ Sponsors and/or investigators may post information about a trial on their website or on central listings of active research. There are several central listings and, in the past several months alone, there have been two announcements of alliances between healthcare websites and clinical trial organizations to post trial information on the Internet.³¹ Information on the Internet may prove particularly beneficial in recruiting for trials involving rare diseases where any one site may have only a small number of eligible subjects in its area.

Investigators told us that they have recently seen more press releases or television news segments describing their research and any promising progress the research may hold. Though not explicitly advertisements, the segments can generate numerous responses.³²

IRB officials and others closely involved with clinical research express many concerns about current recruitment practices

Two-thirds of the IRBs responding to our survey expressed concern about current practices used to recruit human subjects. We not only heard concerns from IRBs, but also from investigators and sponsor representatives. The IRBs had particular concern about those practices that occurred apart from the actual investigator-subject interaction. Their concerns included the financial arrangements between sponsors and investigators (i.e., financial incentives), referral fees, and database searches of private medical information for identifying and recruiting subjects. Both investigators and sponsors raised concerns about the increased pressure to recruit subjects in a timely manner. Many of them spoke of the need to establish a level playing field in the recruitment of subjects in order to avoid a “race to the bottom.” In general, the concerns permeate all four of the recruiting methods we described earlier. At the core, we identified three sets of concerns.

The most fundamental concern is that current practices may contribute to the erosion of informed consent, the foundation of human-subject protections.

In 1978, the National Commission for the Protection of Human Research Subjects laid out the guiding ethical principles still in use today in its report, the *Belmont Report*.³³ The report identified three important elements to informed consent: information, comprehension, and voluntariness. The concerns that IRBs, sponsors, and investigators have about recruitment practices relate, in various ways, to each of these elements.

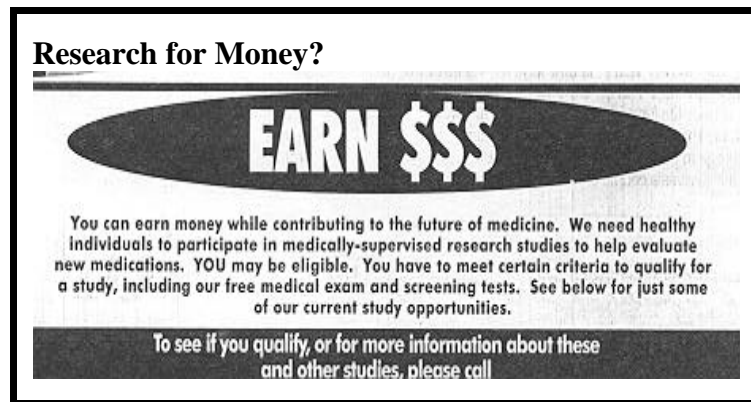
Information. Potential human subjects, the *Belmont Report* makes clear, should have sufficient information that is both accurate and balanced in order to make an informed decision about participation.³⁴ Misleading information may shape subjects’ initial judgment about a research study and, thus, may influence decisions about participating.

IRB officials, investigators, and sponsor representatives consistently expressed their frustration to us over seeing ads they considered misleading. An ad may be misleading, for example, when it implies that an



investigational drug is treatment rather than research (see box). Indeed, many subjects enter research studies with hope of receiving treatment, a phenomenon well-recognized by the industry.³⁵ The blurring of research and treatment, often referred to as “therapeutic misconception,” can be difficult to clarify once a potential subject’s initial impressions have been formed. One coordinator explained that it was difficult for her to field phone inquiries following a news segment about a trial at her research site. She felt that the news segment portrayed the research as a potential cure; callers were eager to join the trial, despite the fact that the research was in its earliest testing stages. Ads also should not overly stress any payment, monetary or otherwise, offered to subjects lest they be considered coercive to the subject (see box below).³⁶ Another concern we heard was about the use of receptionists without clinical expertise who answer 1-800 phone numbers, and serve as the first source of information for potential subjects.³⁷

In the case of national ads, even if IRBs do review an ad and raise questions, many IRBs are concerned that sponsors do not have to respond to their concerns. One IRB official explained a recent situation in which his IRB was asked to review the video of a sponsor-produced television ad. The board had problems with the video because it felt the ad



strongly misrepresented the purpose and potential effect of the investigational material. However, despite repeated communications with the sponsor, the IRB was forced to acquiesce its authority in this matter; the sponsor was not bound to incorporate the changes because a different IRB had already approved the current version of the ad.³⁸ The use of national marketing efforts to recruit is increasing; often the products are flashy, very general and do not reference a specific research site. Consequently, many IRBs are unsure of their authority in reviewing these national ads.

IRBs also have concerns about some newer recruiting methods because the methods are not easily reviewed. News briefs, interviews, or speeches at health fairs call for investigators to speak freely. The focus of the presentation may not be about the research study per se, but the investigator may mention an ongoing study and invite interested people to participate. IRBs are confused over whether these methods actually constitute a recruiting method and what they can or should do after-the-fact.

Comprehension. The way that relevant information is presented to potential subjects is also of vital importance. The *Belmont Report* states, “presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject’s ability to make an informed choice.”³⁹ It is important, therefore, that investigators and their staff convey the information in a way that facilitates potential subjects’ true understanding about a trial’s risks and benefits.

Many people expressed to us their concern that the pressure-filled and competitive research environment may lead investigators or their staff to encourage hesitant subjects to participate.⁴⁰ These concerns were raised particularly regarding financial incentives offered to investigators. According to one survey respondent, financial incentives have the “potential for pressure on/coercion of prospective subjects to enroll.” As one investigator stated, “bonuses are just an incentive for bad behavior.” Although the informed consent document lists the potential risks and benefits of the trial, investigators presenting informed consent documents to subjects may, consciously or subconsciously, distort their descriptions of the trial. As another respondent said, “I worry about what is said to potential subjects.” These concerns are validated by our findings in prior work. We found that IRBs focus a great deal of attention on ensuring that all relevant information is included in the informed consent document, which can run up to 20 pages in length. However, IRBs know little about the interaction between investigator and subject and, thus, how the study is actually presented to potential subjects.⁴¹

The potential significance of industry incentives raises more concerns. Both academic and independent investigators we spoke with expressed the importance that industry monies play in maintaining their position and supporting their research staff. Nonfinancial incentives, such as authorship, may be important for career advancement or tenure decisions at academic institutions. The concerns surrounding these incentives invariably lead to questions about what constitutes adequate disclosure of relevant information. Potential subjects may not understand that investigators are paid or receive a bonus for their participation in a trial.

Voluntariness. Even with accurate information and a balanced presentation, true informed consent, according to the Belmont Report, “requires conditions free of coercion and undue influence.”⁴² We heard significant concerns that the dual role of physician-investigators might infringe upon this voluntariness; concerns worthy of particular attention as we found that investigators often enroll many of their own patients into their

trials. Patients may be reluctant to contradict their doctor's wishes by refusing participation in a trial, or may agree to participate because they trust and respect their physician, who they believe is looking out for their best interests. As one coordinator we spoke with said, "patients see their doctor as God." Another investigator recognized the trust patients hold in their doctors. He told us that he was reluctant to even mention to his patients a trial that involved withdrawing their asthma medications. He was afraid they would agree to participate because he asked them, despite the fact that their current medications were stabilizing their asthma. A Presidential advisory commission went so far as to state that the patients of physician-investigators should be considered a vulnerable population.⁴³

Many ethicists see the doctor-patient relationship as fundamentally different than that of the investigator-subject. In the former, medical care is solely for the benefit of the patient. The investigator-subject model differs in that the subject may or may not benefit from participation in research and the primary interest of the investigator is to develop scientific knowledge.⁴⁴ Some IRBs have recognized these concerns and accordingly enacted policies to distance the physician-investigator from the recruiting process.

The potential influence of physicians on their patients' decision to participate in a trial is particularly troubling for some observers of the clinical research process when the physician receives a fee for referring a patient to a trial.⁴⁵ The concerns focus on the fear that referral fees may lead physicians to further encourage their patients to enter a trial in order to receive a fee. Referral fees are considered unethical by the American Medical Association and by some States; several IRBs and institutions also have policies forbidding their use.⁴⁶

We also heard concerns that people's trust in certain health care professionals could influence their perceived value of the research study being promoted, whether it be on the Internet, television, or elsewhere.

Potential subjects' views and expectations of the research may be altered because they trust the source of the information (see box).⁴⁷ One Internet site, associated with a widely respected former U.S. Surgeon General, received a referral fee for each subject enrolled in a trial through its website; after coming under increasing criticism, he dissolved this reimbursement mechanism.⁴⁸ Another recruiting method we heard about is funneling trial information through disease-support chatrooms on the Internet. In one instance, an investigator went into a chatroom and answered questions about a study, providing the site's name and number, but did not reveal that he was a site representative.

"Done correctly, publicity can look like an endorsement by your well-respected newspaper reporter or TV news anchor. It can be an excellent way to generate phone calls needed to fill studies."

From an industry article on subject recruitment

Concerns about voluntariness are often connected to subject payments as well. Subject payment levels have been studied and most parties involved in clinical research are sensitive to the fact that high payments may lead subjects to enroll in research that they would not participate in otherwise.⁴⁹ As one article mentioned, “it is easier to recruit just before Christmas than in mid-August.”⁵⁰

A second major concern is that, in the rush to recruit subjects, sponsors and investigators may compromise patient confidentiality.

The ease of scanning a patient database to find potential subjects makes the use of these databases very attractive for investigators under pressure to recruit (see box). Most people we spoke with were not concerned about investigators searching through their own patient database to identify eligible subjects. Rather, they were concerned about someone other than the patient’s physician going through medical records and then contacting a patient about participation. Several IRB representatives told us they did not allow their investigators to search any institutional databases, to the frustration of many of the investigators, who assumed that patients had granted access to their records by signing an informed consent document upon admission to the hospital.

Patients often are unaware that their records are being reviewed by persons other than their physician and that these records may be used to contact them about participating in research. Many involved in clinical research believe that patients ought to know who has access to their records and to which records. The Secretary of HHS recently proposed regulations regarding privacy of medical records that may have implications for this recruitment practice.⁵¹

“At present, this group includes 9 cardiologists, 8 cardiovascular surgeons, 3 electrophysiologists, 7 nephrologists, 3 pulmonologists, as well as 7 primary care physicians. This gives XXX Research access to a patient base of over 100,000. Approximately 16,000 of these patients are already in a computerized database, which allows for rapid recruitment.”

“Access to our vast patient database enables us to send direct mail pieces to prospective patients.... Patients are listed according to ICD-9 codes for easy access.”

From site advertisements to sponsors

Physician databases are not the only source of confidentiality concerns; disease registries, school medical records, mailing lists, court records, or other databases have been used to contact subjects.⁵² For example, reporting to some State cancer registries is mandatory. We heard about one State’s registry that is available to any investigator working on a protocol approved by the registry. Yet people listed in registries or other databases may not have consented to being contacted for trial participation.

Concerns about the confidentiality of medical information extend beyond using this information to contact potential subjects. We also heard concerns about confidentiality of personal information collected during the screening of potential subjects. For example,

when call centers are used to pre-screen prospective subjects, callers may be asked their name, contact information, and possibly sensitive information about sexual history or drug use. Potential subjects have little knowledge as to what happens to that information if they are not accepted into the trials. Adequate protections may not be applied to this sensitive information.

IRBs have also received complaints of harassment from potential subjects. OPRR recently cited a research institution when it found investigators participating in harassing recruitment tactics. The potential subjects were recontacted repeatedly despite declining to participate.

Another concern is that pressures on investigators to recruit may lead them to enroll subjects that are ineligible.

Investigators seeking to fulfill a contract with a sponsor and/or ensure future contracts are under constant pressure to find subjects and recruit them quickly. At the same time, investigators face tight eligibility criteria, limiting the eligible pool of potential subjects. Sponsors decide appropriate eligibility criteria jointly with FDA and then inform investigators as to how to determine whether subjects fit these criteria. However, in a competitive environment, research observers fear that, while most investigators will enroll correctly, some investigators may enroll subjects that are ineligible or of questionable eligibility in order to meet quotas and satisfy eager sponsors.⁵³

Although it is difficult to quantify how often ineligible subjects are enrolled into trials, research observers tell us that it happens infrequently; most investigators enroll only eligible subjects. However, what constitutes “eligible” is often hazy; eligibility criteria often involve medical judgment, adding a degree of subjectivity to enrollment decisions. One sponsor monitor told us that some investigators that she has overseen have stretched enrollment criteria, claiming that some used “outrageously bad clinical judgment” just to get subjects into a trial. Another investigator, speaking about the use of incentives, said that if a bonus was set to 30 subjects and a site had 29, “you could bet that the site would get the 30th subject.” But, “I wouldn’t guarantee what you’d find” if someone looked more closely at the subject. Several investigators told us that they had questions about subjects’ true eligibility in some of their trials. Questions arose when the investigators had difficulty finding subjects, and yet other sites were able to enroll great numbers.

The participation of ineligible subjects raises concerns about human-subject safety and data validity. Sponsors include certain exclusion criteria in order to prevent certain people from experiencing adverse reactions and/or to eliminate those at the greatest risk of harm from participating. When sponsors and FDA make decisions regarding a drug’s safety and efficacy, they base their conclusions on the assumption that the drug was tested on the intended population. If these assumptions are false, conclusions of efficacy could be wrong. There are many checks and balances in the clinical research system to uncover ineligible subjects before the trial data has been reviewed by FDA; FDA medical

officers, field investigators, and sponsors' monitors all review subjects' eligibility criteria. Yet, there have been recent cases in which none of these groups discovered that investigators had been enrolling ineligible subjects until after the trials were complete.⁵⁴

Oversight of the recruitment of subjects is minimal and largely unresponsive to emerging concerns

IRBs are not reviewing many of the recruitment practices that they and others find most troubling.

Although financial incentives given to investigators by sponsors to boost enrollment are among the recruitment practices that IRBs are most concerned about, 75 percent of IRBs that responded to our survey do not review any financial arrangements between sponsors and investigators. When IRBs do review subject recruitment practices, they primarily review advertisements and incentives paid to subjects, not practices involving sponsor-investigator interactions.

In addition, 25 percent of IRB survey respondents do not ask investigators to explain recruiting practices in their application for review. The finding that a significant percentage of IRBs do not gather basic information about recruitment practices on their application for review raises the possibility that some IRBs may not be reviewing recruitment practices at all. In addition, of the 23 applications provided by our surveyed IRBs, 13 ask only general questions about recruitment such as, "How will subjects be recruited for the study?" Few inquire about specific recruitment practices in their application for review.

On a positive note, although the IRBs that responded to our survey do not seem to be reviewing the recruitment practices they find most troubling, they claim to be devoting increasing attention to recruitment issues. Sixty-one percent of IRB survey respondents reported that they had requested changes in the recruitment practices called for by a protocol during the past 3 years and many said that they are requesting more of these changes now than 3 years ago. In addition, there has recently been a spate of messages on a listserv for IRB representatives regarding recruitment issues, reflecting both concerns and confusion about many of these issues. Despite lack of guidance from other sources, some IRBs and research institutions have created their own guidelines and policies relating to recruitment (see *Recruiting Human Subjects: Sample Guidelines for Practice*, OEI-01-97-00196), even though more stringent reviews may put these IRBs at a competitive disadvantage because the reviews take longer.

IRBs' limited review of recruitment practices is in part due to their perceived lack of authority to review certain practices.

IRBs may not be reviewing some recruitment practices because they do not believe that they have the authority to do so, or are uncertain of their authority. Our survey indicates that, while IRBs are confident about their authority to review advertisements for recruiting subjects and subject incentives, both explicitly mentioned in FDA guidance to IRBs, they are much less confident about their authority to review other recruitment methods. IRBs can draw their authority to review protocols from sources other than Federal regulations and guidelines, such as institutional policy. Yet, any steps that an IRB were to take toward establishing more stringent protocol reviews would be unpopular among the researchers in that institution. Given the competitive nature of the current research environment, such added stringency would put the IRB at competitive disadvantage.

IRBs' perceived authority to review different recruitment practices

Recruiting Strategy	Method	Clearly Have the Authority	Are Uncertain of Authority	Clearly Don't Have the Authority
Offering Incentives	Authorship incentives	24%	42%	34%
	Financial incentives to investigators	43%	32%	26%
Targeting One's Own Patients	Review of investigators' own patient databases	60%	16%	24%
Seeking Additional Patient Bases	Review of <i>other</i> physicians' databases to identify/contact eligible subjects	66%	17%	17%
	Referral fees	65%	25%	10%
Advertising and Promotion	Print ads	96%	3%	1%
	Radio/TV scripts	92%	7%	1%
	Internet ads	83%	15%	2%
	Subject payments	92%	5%	3%
	Receptionist scripts	64%	28%	9%

Source: OEI survey, 1999.

HHS provides little clear guidance to IRBs on acceptable recruitment practices. In contrast, some professional medical associations provide strong guidance on selected issues.

FDA. The primary guidance to IRBs comes from the FDA in the form of *Information Sheets*. Two *Information Sheets* relate specifically to recruitment issues, “Recruiting Study Subjects” and “Payment to Research Subjects” (see appendix B for the complete text of these documents). “Recruiting Study Subjects” gives IRBs blanket authority to “review the methods and material that investigators propose to use to recruit subjects,” but does little to explain how methods ought to be reviewed.

The *Information Sheets* also fail to mention many recruitment methods that are currently in use. The *Sheets* focus solely on methods that come into direct contact with potential subjects, such as advertisements, payments to subjects, and receptionist scripts. Notably absent from the *Information Sheets* is any guidance regarding methods that are “invisible” to subjects, such as how physician-investigators should handle their dual role when recruiting their own patients. Similarly, the *Sheets* fail to mention anything about investigators or others accessing names of potential subjects (with identifiable medical information), through electronic databases or medical charts, to contact about trial participation. Finally, the *Sheets* do not consider what types and degrees of financial incentives constitute a potential conflict of interest. The FDA recently began requiring investigators to disclose to the Agency some of the investigators’ financial arrangements with sponsors, evidence that FDA believes that a certain level of financial interest is relevant to the Agency’s own scientific review.⁵⁵

One of the most confusing issues not addressed in the *Information Sheets* is recruitment practices in multi-site trials. Sponsors, IRBs, and sites all reported being uncertain about some aspect of recruitment for these trials. IRBs were uncertain of their authority to change ads or telephone scripts on a multi-site trial if another IRB had already approved it. Private sites that used different IRBs for different trials complained about a lack of consistent guidelines for IRB review of ads and other recruitment materials; certain wording that was forbidden by one IRB might be required by another. Sponsors faced this same frustration when they tried to create an ad that would be acceptable to all of the IRBs in a multi-site trial.

NIH/OPRR. OPRR has a Guidebook for IRBs that discusses a variety of recruitment issues not mentioned in the FDA *Information Sheets*.⁵⁶ But, the Guidebook relies on the *Information Sheets* for specific guidance on recruiting practices. For example, the Guidebook draws attention to possible conflicts when the investigator is also the subject’s physician and to concerns of coercion when the trial offers free health care. It also mentions concerns regarding searching databases for potential subjects and then contacting these subjects about participating in the trial. However, the Guidebook fails to advise IRBs as to whether these practices should be allowed or how they ought to be

reviewed, nor does the Guidebook link these issues explicitly with recruiting practices. For instance, in discussing the practice of following up a letter requesting participation with a phone call, the Guidebook merely states, “IRBs should be sensitive to this concern.”⁵⁷

Other Sources. Federal oversight bodies are not the only sources of guidance available to IRBs. Many investigators and IRB members are members of professional medical associations that provide some additional guidance on recruitment issues. In our review of 20 medical associations’ codes of ethics and position papers, we found that some associations have strong, explicit guidelines on certain recruitment issues (see appendix C and our companion report). For example, the American Academy of Neurology acknowledges the trust relationship that patients have with their doctors, especially in cases where patients are particularly vulnerable, such as people with severe, progressive, or terminal illnesses. Under such circumstances, the Academy claims that the “distinction between medical care and experimental treatment may become blurred.”⁵⁸ It further suggests that researchers and IRBs take special precautions, perhaps by requesting that an “uninterested” party explain the research to the potential subject. The American College of Emergency Physicians states that industry payments to investigators should be disclosed.⁵⁹

Many other associations have general guidelines about medical practice that could be extrapolated to the practice of research. For instance, many professional medical associations prohibit the use of patients’ private medical information for any purposes other than diagnosis and treatment, unless the patient has given express permission.⁶⁰ Such a position could be interpreted to mean that these associations do not condone the use of private medical information for contacting subjects about trial participation.

In their own oversight of research sites, sponsors pay minimal attention to how human subjects are recruited.

Although IRBs’ central mission is to oversee human-subject protections, sponsors have responsibility for the ongoing safety of subjects in their trials. The FDA states that the “sponsor is responsible for assuring throughout the clinical investigation that the investigators’ obligations, as set forth in applicable regulations, are being fulfilled.”⁶¹ In fulfilling this responsibility, sponsors may officially delegate clinical trial monitoring responsibilities to a CRO.⁶² Sponsors or CROs oversee investigators, and in turn, the protection of human subjects, almost exclusively through their monitors.

We found, in speaking with monitors and investigators, that monitors focus on ensuring the quality of data, rather than human-subject protections. Although monitors will often verify that advertisements have been approved by the site’s IRB, they do not verify IRB approval of some of the recruitment methods that raise the most concerns. Monitors visit the research site frequently and may learn of practices that raise concern. Yet, according to monitors and sponsor representatives, even if a monitor were to discover that an

investigator was doing something that raised concern, the monitor may be discouraged by his/her superiors from taking any action, particularly if the investigator in question were a prestigious one.⁶³ Furthermore, sponsors initiate many of the practices that raise the most concerns, such as enrollment bonuses and authorship incentives, thus undermining their ability to oversee research sites' recruitment practices effectively.

Nor does HHS pay much attention to recruitment practices in their inspections of IRBs and investigators.

The FDA routinely inspects investigators and IRBs under the Bioresearch Monitoring Program. Its objectives for conducting investigator inspections are, "ensuring the quality and integrity of data and information submitted to FDA as well as the protection of human research subjects."⁶⁴ However, our review of FDA's inspection process for clinical investigators revealed that the FDA's main focus is on the former, ensuring the integrity of data submitted to the Agency.

The FDA's stated purpose in inspecting IRBs is "to determine whether an IRB is operating in accordance with its own written procedures as well as in compliance with current FDA regulations affecting IRBs."⁶⁵ In our review of FDA's inspection process for IRBs, we found that FDA focuses on procedural compliance, not the content of IRB reviews.

Neither the IRB and investigator inspection protocols, nor the inspections themselves, consider how investigators recruit or ensure that IRBs oversee recruitment. The one exception involves ads. Both the investigator and IRB inspection protocols instruct FDA inspectors to determine whether any recruitment advertisements had been approved by the site's IRB before subjects were allowed to participate in the trial.

Not only are FDA inspections of investigators and IRBs limited in scope, but they are also limited in number, particularly at foreign research sites. The Center for Drug Evaluation and Research conducted 179 IRB inspections in 1998, out of a universe of roughly 3,000-5,000 IRBs.⁶⁶ Despite the large number of foreign trials, the FDA normally does not inspect foreign IRBs.⁶⁷ In that same year, 1998, CDER conducted 348 investigator inspections, of which 60 were conducted abroad.

OPRR conducts many fewer inspections than FDA and conducts them primarily for cause. Unlike FDA, OPRR lacks a written inspection protocol that would enable us to determine exactly what they consider in its IRB inspections. Since most of OPRR's inspections are for cause, its inspections are focused according to the problem at hand. Occasionally, those on-site reviews will address and raise concerns about recruitment practices. In at least one of OPRR's recent inspections, OPRR faulted the IRB for inadequate review of a protocol's recruitment methods and required the IRB to establish "subject enrollment procedures that minimize the possibility of coercion or undue influence" in order to be allowed to continue conducting federally funded research.

RECOMMENDATIONS

There is a compelling national need to recruit human subjects to participate in clinical research — a need vital to the continued progress and discovery of new, effective drugs. But, there is a danger that this imperative could compromise the protection of human subjects. Our inquiry reveals significant vulnerabilities concerning the recruitment of subjects. It also reveals that IRBs, the Federal government, and sponsors have been doing little to address the recruitment practices that generate the most concern.

It is in the best interest of all involved in the research enterprise to address concerns about recruitment practices. In a highly competitive marketplace, with few rules or guidelines governing recruitment, there is a very real danger of a race to the bottom. Some sponsors and investigators may find it difficult to refrain from recruitment practices that are effective in delivering a steady stream of subjects to participate in clinical trials. But, these recruitment practices could compromise long-valued human-subject protections. A groundswell of concern over certain recruitment strategies, or negative publicity over an unfortunate event, would undoubtedly lower public confidence in clinical research and, in turn, heighten the difficulty many sponsors and investigators experience in recruiting subjects.

The critical challenge, then, is to achieve some balance — to ensure essential human-subject protections without unnecessarily slowing the pace of research and discovery. This challenge is especially significant since IRBs, which serve as the main source of protection, are themselves in danger. As we have shown in a previous report, they are increasingly overburdened, have limited helpful information, and often have inadequate resources.

Below we offer four main recommendations. The first two are specifically pertinent to the concerns raised about current practices used to recruit human subjects. The third and fourth recommendations, which stem from our prior work on IRBs, are aimed at improving human-subject protections more generally, but are integral to the issues of subject recruitment.

We present these recommendations jointly to FDA, NIH, and the Assistant Secretary of Health (ASH). We include ASH because the Secretary recently decided that OPRR be moved to the Office of Public Health and Science, within the Office of the Secretary, with a direct reporting line to the Assistant Secretary for Health. In those instances where we present a recommendation to only one of the agencies, we specify the agency directly.

We should also note that, although our methodology focused on drug research, we expect that our findings and recommendations would also be relevant to other types of clinical research (including clinical research on medical devices or biologics).

1. Provide IRBs with direction regarding oversight of recruitment practices

1a. Clarify that IRBs have the authority to review recruiting practices

The most important step that Federal bodies should take is to *clarify* that IRBs have the authority to review recruiting methods. Our review found that IRBs are uncertain of their authority to review recruiting practices, some of which raise significant concerns about the adequacy of the informed consent process.

Federal regulations state that informed consent may be sought “only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.”⁶⁸ IRBs have the authority to ensure informed consent of human subjects. Similarly, Federal regulations require IRBs to review and approve the initiation and conduct of covered biomedical research activities involving human subjects. This broad mandate also provides a basis for IRBs to review practices for recruiting human subjects.

Federal bodies should explicitly indicate in their guidance that certain practices that may only *indirectly* impact subjects, such as investigator incentives, also fall under IRB purview, as they may affect the informed consent process. FDA and NIH should disseminate this guidance promptly. The focus of current Federal guidelines and IRB oversight is on recruiting practices that directly affect potential subjects. IRBs most often review advertisements or subject payments, the subject of the two FDA *Information Sheets*.

1b. Provide guidance to IRBs on how to exercise this authority

FDA and OPRR should assist IRBs in their review of recruiting practices by suggesting questions that boards should address and by fostering discussion of the issues by IRBs at the local level. A simple statement outlining IRB authority to review recruiting practices is inadequate. Throughout its IRB Guidebook, OPRR does propose that IRBs pay attention to issues such as subject confidentiality and doctor-patient influence. However, these issues should be more closely linked with the review of recruiting practices. This guidance would be of immediate value to IRBs in their review of protocols, as many IRBs are extremely conscientious of their responsibilities as outlined in Federal regulation and guidance. Such direction will allow IRBs to take steps in their oversight previously considered unnecessary, murky, or intrusive.

2. Facilitate development of guidelines for all parties on appropriate recruiting practices

We recognize that the concerns raised about current recruiting practices include many gray areas where opinions differ on appropriate practices. Thus, it is essential to involve an adequate representation of the key participants — sponsors, industry groups, investigators, IRB representatives, patient advocates, ethicists, and other parties (such as the Institute of Medicine) — in a process that addresses the concerns and seeks to develop consensus on appropriate practices. Such discussions are vital to assisting Federal bodies in developing further recruitment guidance, thereby maintaining adequate human-subject protections.

A clearer determination of *appropriate* recruiting practices would be helpful for all parties — sponsors, investigators, and IRBs. Understanding the appropriateness of certain practices can be helpful for sponsors and investigators as they recruit subjects and for IRBs in their reviews. Recently, there have been forums convened considering standards for medical Internet sites.⁶⁹ Further Federal guidance on appropriate recruiting practices will help to ensure a level playing field in the competitive clinical research marketplace.

As part of their deliberations, the groups should seek consensus on questions such as:

- ▶ Is it acceptable for sponsors to offer bonuses to investigators for successfully recruiting subjects?
- ▶ Should physicians be allowed to receive fees for referring their patients as potential subjects for a clinical trial?
- ▶ Should the financial arrangements between sponsors and investigators be disclosed to potential subjects?
- ▶ Does searching medical records for potential subjects constitute a breach of confidentiality?

In addition, a greater understanding of already established guidelines and their impact would be helpful to the deliberating groups, including Federal bodies, as they develop guidance on appropriate practices. The groups could research the existing guidelines and policies on issues not currently addressed in the FDA *Information Sheets*, many of which are already adhered to at local research institutions or in other countries.⁷⁰ For example, they could assess what prompted these research institutions, foreign regulatory agencies, and medical professional associations to develop such guidelines or policies, any barriers that these entities have encountered in implementing these guidelines/policies, and how their members/investigators responded to them.

3. Ensure that IRBs and investigators are adequately educated about human-subject protections

3a. Require education for investigators before conducting human-subjects research

An education requirement could be a prerequisite for signing an investigator-agreement form (known as a 1572) to participate in research under FDA regulation or for receiving Public Health Service Act funds for conducting human-subject research. Investigator education is of particular importance because investigators and their staff are the ones who actually interact with potential subjects and often lead recruiting efforts. Also, there are an increasing number of new, inexperienced investigators participating in clinical research. At least one research institution has created a human-subject protection training requirement for its investigators.

3b. Require that IRBs have a training program for board members

Because of their vital roles as the primary source of human-subject protections, IRB members must have adequate training that highlights the issues surrounding the recruitment of human subjects. IRB education could inform members of current recruiting practices and could raise their awareness of concerns about these when conducting their reviews.

3c. Require more extensive representation on IRBs of nonscientific and noninstitutional members

The requirement of at least one noninstitutional and one nonscientific member out of five members should be interpreted as a ratio. IRBs often have 15 or more members and the requirement can be fulfilled with the appointment of just 1 person. Nonscientific and noninstitutional members on IRBs can further ensure that IRBs are sensitive to human-subject protection issues; lay members' voices provide an important balance to institutional interests on an IRB. Because many recruiting concerns raise issues about what a typical subject would wish to know in order to make an informed decision or what constitutes a breach of confidentiality, the perspectives of independent lay members are of particular importance.⁷¹

4. Strengthen Federal Oversight of IRBs

4a. Require that all IRBs register with the Federal government and regularly report basic descriptive information

Federal oversight could be strengthened if IRBs were required to submit, at a minimum, brief descriptive information including location and contact person. Such information would be extremely helpful in disseminating guidance and targeting effective oversight, such as inspections. FDA has begun the process of developing such a registration system. We also suggest that there be one registration system for all HHS agencies involved in human-subject protection oversight, further facilitating communication and oversight efforts between the agencies.

FDA has a database of IRBs identified on the investigator-agreement form submitted to review Investigation New Drug research, but the database is limited. We used the FDA database to identify IRBs for our survey. A significant percentage of the surveys were returned to sender or the contact person called us to say that they had never heard of the IRB or were never involved with its reviews. These limitations of FDA's IRB database are particularly important because recruitment guidance for IRBs would be disseminated using the database, thus raising the possibility that a large number of IRBs would not receive such critical guidance.

4b. Revamp the FDA on-site inspection process

In FDA's inspections, primarily the clinical-investigator inspections, the Agency could address many of the concerns about recruiting methods and raise questions about how human subjects were recruited. Inspectors could consider assessing the range in number of subjects enrolled across sites. If, for example, one site enrolled significantly more subjects than other sites or financial incentives were offered by sponsors, inspectors could probe to understand how these subjects were enrolled and why the high-enrolling site was able to recruit when others were unsuccessful. Also, at these high-enrolling sites, inspectors could examine more closely whether enrolled subjects were truly eligible.

Comments on the Draft Reports

We received comments on our two draft reports from the Department of Health and Human Services (HHS). We also solicited and received comments from the following external organizations: Public Citizen’s Health Research Group, Pharmaceutical Research and Manufacturers of America (PhRMA), Applied Research Ethics National Association (ARENA) in conjunction with Public Responsibility in Medicine & Research (PRIM&R), and the Consortium of Independent Review Boards (CIRB). We did make a number of changes in the final reports, many technical in nature, that respond to their comments. We include the complete text of the comments in appendix D. Below we summarize the major comments and offer our response to HHS and, collectively, to the external parties.

HHS Comments

We appreciate both HHS’ positive response to our reports and its commitment to address the issues raised in our findings and recommendations. We are particularly encouraged by HHS’ commitment to establish new requirements for human-subject protection education. As the primary bodies for subject protections, IRBs must be adequately educated about ethical issues in order to ensure protections. Investigators interact directly with subjects and therefore, must be attuned to protection issues and concerns. We note here also, that through the course of this study, we became increasingly aware of the fact that investigators’ staff interact with subjects much more so than investigators. We urge HHS to recognize the increasing importance of investigators’ staff in their efforts.

We particularly welcome, too, HHS’ (through FDA, NIH, and the new Office of Human Research Protections) willingness to work with all parties in clinical research to develop guidance on appropriate recruiting practices. As we noted in our recommendations, it is essential that all parties be involved in this consensus-building process. The Department, and particularly NIH, is a well-recognized leader in the field of clinical research and is well-positioned to take a leading role in this important area.

We acknowledge in the report that both FDA and NIH have current guidance documents highlighting the recruitment of human subjects. However, we found in our survey that many IRBs remain unsure of their authority to review recruiting practices and, therefore, further guidance is needed. Clearer guidance is especially important because IRBs may face pressure to provide a timely review of protocols. In reassessing the current IRB guidance, we urge HHS to consider our recommendation that IRBs be provided guidance *clarifying* their authority in this area. The guidance need not be a laundry list of how to review each individual practice, rather a reminder that IRBs already have the authority. This guidance would also serve as a recognition that recruiting practices can impact human-subject protections.

Through its assurance process, OPRR does have identifying information on the IRBs it oversees. With the move to the Office of the Secretary and the new office's central role in representing the Department, we urge the new office and FDA to combine its efforts to create one repository for information and contacts for all IRBs involved in HHS activities. As HHS acknowledges in its comments, this information will facilitate more effective education and oversight.

External Parties' Comments

Overall, we were pleased that external parties echoed the concerns we raised about some current practices for recruiting subjects into clinical trials and that steps should be taken to identify, at a national level, appropriate recruitment practices. The following are common points raised in the external parties' comments to our report:

Consensus about appropriate recruitment practices must be forged among all parties.

A number of parties raised concerns that our recommendations would call for Federal bodies to dictate appropriate recruiting practices without input from outside groups. These are not easy questions and there are not easy answers. Thus, we have recommended that all of the different parties involved in clinical research, including Federal oversight bodies, sponsors, investigators and IRBs, search for reasonable consensus on appropriate practices. We hope that the concerns we raise in this report provide the impetus for discussions on appropriate practice.

Other entities must share the responsibility for overseeing recruitment practices with IRBs.

Many voiced concern that IRBs are already overburdened and, therefore, it would be unwise to add to their duties. We share this concern, but do not believe that the recommendations laid out in this report would necessarily require more work on the part of the IRB. First, just as we believe that decisions about appropriate recruitment practices should be arrived at jointly, we believe that the oversight of these practices should be a shared responsibility. Presumably, as consensus develops, sponsors and investigators will be more aware of which recruitment practices are appropriate and will refrain from engaging in them, making the IRB's job easier. In addition, many IRBs already do review recruitment practices, but, because of a lack of clear guidance, this review can entail much debate. If clear guidance existed, such debate could be minimized. Ultimately, if recruitment practices are occurring that could potentially harm human subjects, then these concerns must be addressed, whether by the IRB or other entities, regardless of time and resource constraints. Perhaps some of the Federal IRB regulations could be revamped to allow IRBs greater flexibility to review issues that have direct impact on human-subject protections, as suggested in a prior report.

Clarifications on our Methodology

Several points were raised about our methodology. In this report, we sought to document current practices used to recruit human subjects and identify any concerns associated with these practices. We did not seek to judge the appropriateness of any given recruitment practice. We also focused on industry-sponsored trials and therefore are not in a position to determine whether recruitment practices vary by funding source. We should note that much of our information was provided by investigators who were involved in research from different funding sources. It is possible that the investigators in talking with us may not have distinguished their research by funding source.

Because of the variety of disease types, potential subject groups, phase of trial, and other factors specific to each protocol, we had to rely primarily on qualitative evidence, obtained through site visits and interviews with key stakeholders. There would have been no feasible way to conduct this study in a strictly data-driven manner. We drew from common themes that arose during the course of this study, using examples to illustrate these themes.

Our IRB survey respondents included all types of IRBs: independent, hospital-based and academic IRBs. We did not consider the differences among these types of IRBs. There were no significant differences in responses to our survey when stratified by domestic versus foreign IRBs. We believe our findings and recommendations should apply to all types of IRBs.

Answers to specific comments

Registration of IRBs. ARENA raised concerns that our recommendation that IRBs register with FDA would add a burden to IRBs with little benefit. We believe that registration would allow FDA to provide guidance to all IRBs in an efficient, streamlined fashion. Because the Agency has limited and sometimes inaccurate information about the IRBs it oversees, its ability to disseminate guidance in a way that ensures that all IRBs will receive it is jeopardized. The registration process need not be a significant burden to an already overtaxed IRB system; the process could involve IRBs providing minimal descriptive information to FDA (i.e., location, address, contact person and number).

Education Requirements. We agree with PhRMA that education of investigators, IRBs and sponsors should not be a “one-size-fits-all” model. Our recommendation calls for an education requirement. However, we do not intend to suggest that there should be a national standardized educational program. The substance of the education may vary according to the party it is geared towards. The important thing is that all of the parties are educated, as a prerequisite for taking part in FDA-regulated research.

Methodology

IRB Survey

We surveyed a total of 200 IRBs. We selected the random sample of IRBs identified through the FDA Investigational New Drug database. In an attempt to ensure that our respondents had adequate and recent experience to draw on and to improve the response percentage, the sample included only those IRBs involved in four or more IND trials in 1997 and 1998 and those that identified a contact person. Of the 624 remaining unique IRBs in this group, we randomly selected 150 U.S.-based IRBs and 50 foreign IRBs.

The surveys focused on any experiences or concerns they may have about any recruitment techniques and the extent and nature of their oversight. We received responses from 108, or 54 percent, of the IRBs we sampled.

Review of FDA and OPRR Oversight Processes

We reviewed each office's oversight processes to determine whether and to what extent they address subject recruitment issues. For FDA, we reviewed the Bioresearch Monitoring inspection protocols for both IRBs and investigators. In addition, we accompanied FDA inspectors on the routine inspection of both a clinical investigator and an IRB. We observed the inspection process and reviewed files for IND clinical trials seeking information on subject recruitment. For OPRR, we examined the assurance process, reports from previous inspections, and its IRB Guidebook.

In-depth Site Visits

We visited five research sites, both academic and independent, to learn about individual investigators' and research staff's experiences recruiting subjects. We chose the sites based on their research activity, location, and our ease of access to the research community. In each of the institutions, we interviewed, among others, research investigators; research coordinators and nurses; IRB administrators and members; and institution administrators.

Review of Existing Guidelines

We collected relevant ethics codes or guidelines from 20 professional medical associations, numerous IRBs, and Canada. We then reviewed these guidelines to determine their applicability to the recruitment of subjects.

Analysis of Data in IND Database

We analyzed the FDA Center for Drug Evaluation and Research's Investigational New Drug database, current as of July 29, 1999, by importing the database into SAS to identify trends in, for example, the selection of sites and the activity of research investigators.

Interviews with Key Parties

We interviewed representatives of groups with national perspectives on recruitment issues, including: sponsors, CROs, SMOs, patient recruitment firms, IRBs, and ethicists.

Literature and Document Review

We reviewed relevant literature, including Federal documents, scientific and trade literature, the lay press, and relevant websites, for information on the issues surrounding recruitment.

FDA Information Sheets

GENERAL

RECRUITING STUDY SUBJECTS

▶ RECRUITING STUDY SUBJECTS

FDA requires that an Institutional Review Board (IRB) review and have authority to approve, require modifications in, or disapprove all research activities covered by the IRB regulations [21 CFR 56.109(a)]. An IRB is required to ensure that appropriate safeguards exist to protect the rights and welfare of research subjects [21 CFR 56.107(a) and 56.111]. In fulfilling these responsibilities, an IRB is expected to review all the research documents and activities that bear directly on the rights and welfare of the subjects of proposed research. The protocol, the consent document and, for studies conducted under the Investigational New Drug (IND) regulations, the investigator's brochure are examples of documents that the IRB should review. The IRB should also review the methods and material that investigators propose to use to recruit subjects.

A. Media Advertising:

Direct advertising for research subjects, i.e., advertising that is intended to be seen or heard by prospective subjects to solicit their participation in a study, is not in and of itself, an objectionable practice. Direct advertising includes, but is not necessarily limited to: newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects. *Not included are:* (1) communications intended to be seen or heard by health professionals, such as "dear doctor" letters and doctor-to-doctor letters (even when soliciting for study subjects), (2) news stories and (3) publicity intended for other audiences, such as financial page adver-

tisements directed toward prospective investors.

IRB review and approval of listings of clinical trials on the internet would provide no additional safeguard and is not required when the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information. Examples of clinical trial listing services that do not require prospective IRB approval include the National Cancer Institute's cancer clinical trial listing (PDQ) and the government-sponsored AIDS Clinical Trials Information Service (ACTIS). However, when the opportunity to add additional descriptive information is not precluded by the data base system, IRB review and approval may assure that the additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the protocol and the informed consent document.

FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process. Advertisements should be reviewed and approved by the IRB as part of the package for initial review. However, when the clinical investigator decides at a later date to advertise for subjects, the advertising may be considered an amendment to the ongoing study. When such advertisements are easily compared to the approved consent document, the IRB chair, or other designated IRB member, may review and approve by expedited means, as provided by 21 CFR 56.110(b)(2). When the IRB reviewer has doubts or other complicating issues are involved, the advertising should be reviewed at a convened meeting of the IRB. FDA expects IRBs to review the adver-

tising to assure that it is not unduly coercive and does not promise a certainty of cure beyond what is outlined in the consent and the protocol. This is especially critical when a study may involve subjects who are likely to be vulnerable to undue influence. [21 CFR 50.20, 50.25, 56.111(a)(3), 56.111(b) and 812.20(b)(11).]

When direct advertising is to be used, the IRB should review the information contained in the advertisement and the mode of its communication, to determine that the procedure for recruiting subjects is not coercive and does not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol. The IRB should review the final copy of printed advertisements to evaluate the relative size of type used and other visual effects. When advertisements are to be taped for broadcast, the IRB should review the final audio/video tape. The IRB may review and approve the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording. The review of the final taped message prepared from IRB-approved text may be accomplished through expedited procedures. The IRB may wish to caution the clinical investigators to obtain IRB approval of message text prior to taping, in order to avoid re-taping because of inappropriate wording.

No claims should be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic or device. Such representation would not only be misleading to subjects but would also be a violation of the Agency's regulations concerning the promotion of investigational drugs [21 CFR 312.7(a)] and

of investigational devices [21 CFR 812.7(d)].

Advertising for recruitment into investigational drug, biologic or device studies should not use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational. A phrase such as "receive new treatments" leads study subjects to believe they will be receiving newly improved products of proven worth.

Advertisements should not promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation. Advertisements may state that subjects will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type.

Generally, FDA believes that any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements. It should be noted, however, that FDA does not require inclusion of all of the listed items.

1. the name and address of the clinical investigator and/or research facility;
2. the condition under study and/or the purpose of the research;
3. in summary form, the criteria that will be used to determine eligibility for the study;
4. a brief list of participation benefits, if any (e.g., a no-cost health examination);
5. the time or other commitment required of the subjects; and
6. the location of the research and the person or office to contact for further information.

B. Receptionist Scripts:

The first contact prospective study subjects make is often with a receptionist who follows a script to determine basic eligibility for the specific study. The IRB should assure the procedures followed adequately protect the rights and welfare of the prospective subjects. In some cases personal and sensitive information is gathered about the individual. The IRB should have assurance that the information will be appropriately handled. A simple statement such as "confidentiality will be maintained" does not adequately inform the IRB of the procedures that will be used.

Examples of issues that are appropriate for IRB review: What happens to personal information if the caller ends the interview or simply hangs up? Are the data gathered by a marketing company? If so, are names, etc. sold to others? Are names of non-eligibles maintained in case they would qualify for another study? Are paper copies of records shredded or are readable copies put out as trash? The acceptability of the procedures would depend on the sensitivity of the data gathered, including; personal, medical and financial.

Also see FDA Information Sheets: "A Guide to Informed Consent Documents" and "Payment to Research Subjects."

▶ PAYMENT TO RESEARCH SUBJECTS

The Institutional Review Board (IRB) should determine that the risks to subjects are reasonable in relation to anticipated benefits [21 CFR 56.111(a)(2)] and that the consent document contains an adequate description of the study procedures [21 CFR 50.25(a)(1)] as well as the risks [21 CFR 50.25(a)(2)] and benefits [21 CFR 50.25(a)(3)]. It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug, biologic or device development. Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive. Financial incentives are often used when health benefits to subjects are remote or non-existent. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence [21 CFR 50.20].

Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn. For example, in a study lasting only a few days, an IRB may find it permissible to allow a single payment date at the end of the study, even to subjects who had withdrawn before that date.

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

Also see FDA Information Sheets: "A Guide to Informed Consent Documents" and "Recruiting Study Subjects."

Professional Medical Association Guidelines

The following chart indicates which medical associations have such guidelines or codes of ethics. Guidelines that specifically pertain to clinical trials are denoted by a ✓. Associations that have general medical practice guidelines or codes of ethics that could have *implications* for clinical research are denoted by a ✪.

Professional Association	Associations' Guidelines or Codes of Ethics							
	Incentives			Dual Role	Confidential Records	Other Guidance		
	Referral fees	Disclosure to subjects of financial arrangements	Compensation to investigators for conducting clinical trial	Dual investigator-physician role	Use of medical records for identifying /contacting potential subjects	Advertisement/ payment to subjects	News briefs	
American Academy of Allergy, Asthma and Immunology								Also defers to other sources of guidance
American Academy of Family Physicians	✪				✪			
American Academy of Neurology				✓				
American Academy of Ophthalmology		✪	✪					
American Academy of Orthopaedic Surgeons		✪	✓					AMA Code of Ethics
American Academy of Pediatrics			✓			✓		
American Academy of Physical Medicine and Rehabilitation	✪							Nuremberg laws
American Association of Neurological Surgeons					✪			

Professional Association	Associations' Guidelines or Codes of Ethics						
	Incentives		Dual Role	Confidential Records	Other Guidance		Also defers to other sources of guidance
	Referral fees	Disclosure to subjects of financial arrangements for conducting clinical trial	Dual investigator-physician role	Use of medical records for identifying/contacting potential subjects	Advertisement/payment to subjects	News briefs	
American College of Emergency Physicians	✱	✓					
American College of Obstetricians and Gynecologists		✱					
American College of Physicians	✓		✱	✓	✱	✓	
American College of Radiology		✱					
American College of Surgeons	✱	✱					
American Geriatrics Society							
American Medical Association	✓				✱	✓	
American Women's Medical Association							
American Pharmaceutical Association							
American Psychiatric Association	✱	✓			✱		AMA Code of Ethics
American Society of Anesthesiologists					✱		AMA Code of Ethics
American Society of Plastic and Reconstructive Surgeons	✱	✱					
National Medical Association							

Comments on the Draft Reports and OIG Response

In this appendix, we present the full comments of all parties that responded to our two draft reports. In order, the comments that we present in this appendix are from the following parties:

- ▶ The U.S. Department of Health and Human Services
- ▶ Public Citizen’s Health Research Group
- ▶ Pharmaceutical Research and Manufacturers of America
- ▶ Applied Research Ethics National Association (in conjunction with Public Responsibility in Medicine & Research)
- ▶ Consortium of Independent Review Boards



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington, D.C. 20201

26 May 2000

MEMORANDUM TO: George Grob
Deputy Inspector General for Evaluations and Inspections

FROM: William Raub *William F Raub*
Deputy Assistant Secretary for Science Policy

SUBJECT: OIG Report on Recruitment of Human Research Subjects

The Office of the Secretary, HHS appreciates the opportunity to comment on the Office of the Inspector General (OIG) report entitled "Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research". We are concerned that some contemporary recruitment practices may put potential subjects at unnecessary risk. Moreover, we note that such risk could be reduced to a minimal level if Institutional Review Boards (IRBs) were uniformly diligent in their oversight of recruitment practices. HHS has a responsibility to provide IRBs guidance that helps them meet this challenge.

The remainder of this memorandum is divided into two parts. The first part contains our comments on the specific recommendations in the subject report. The second part contains information on new and ongoing IHS actions to protect human research subjects. We believe this additional information is strongly relevant not only to the subject report but also to earlier related ones issued by OIG.

SPECIFIC COMMENTS ON THE SUBJECT REPORT

1. Provide IRBs with direction regarding oversight of recruitment practices.

Clarify that IRBs have the authority to review recruiting practices.

Provide guidance to IRBs on how to exercise this authority.

Current guidance documents issued by the Office for Protection from Research Risks (OPRR), National Institutes of Health (NIH) and the Food and Drug Administration (FDA) make clear that IRBs have responsibility for oversight of recruitment practices. For example, FDA has an Information Sheet entitled "Recruiting Study Subjects". Following the imminent elevation of human subjects protection functions from the OPRR/NIH to the Office of the Secretary and appointment of a Director for the relocated unit, HHS will assess the current guidance related to IRB oversight of recruitment practices and augment it as appropriate. We agree that this effort warrants high priority.

2. Facilitate development of guidelines on appropriate recruiting practices.

In concert with their joint and individual efforts to protect human research subjects, OPRR, FDA, and NIH will work with professional societies and others to identify exemplary recruitment practices and incorporate them into guidance, either directly or by reference, as appropriate.

3. Ensure that IRBs and investigators are adequately educated about human-subjects protections.

*Require education for investigators before conducting human-subjects research.
Require that IRBs have a training program for board members.
Require more extensive representation on IRBs of nonscientific and noninstitutional members.*

HHS will institute new requirements for continuing education regarding the protection of human research subjects. NIH and FDA will ensure that authorized curricula are consistent with International Conference on Harmonizations (ICH) guidelines on Good Clinical Practice in Clinical Research, which already are promoted by FDA and its counterpart regulatory agencies of nations within the European Union and Japan. The continuing education requirement will apply to investigators, IRB members and staff, and other officials involved in regulatory compliance.

4. Strengthen Federal oversight of IRBs.

*Require that all IRBs register with the Federal government and on a regular basis report minimal descriptive information.
Revamp the FDA on-site inspection process.*

OPRR has identifying information on all the IRBs associated with the assurances it has negotiated with research institutions. A research institution must have an acceptable assurance on file with OPRR before it may undertake human subjects research funded by HHS agencies. Institutions with OPRR-approved assurances usually apply the terms of their assurances to all their research with human subjects, irrespective of sponsor.

FDA is developing a plan to register the IRBs for which it has cognizance and will implement this plan as resources allow. The FDA effort will include collaboration with OPRR toward ensuring efficiency and avoiding undue duplication of effort. We believe that registration of IRBs not only will enable HHS agencies to provide more effective education and oversight but also will be an important step in developing an accreditation process for institutional systems designed to protect human research subjects.

During the last several years, FDA has stepped up its on-site inspection process significantly. FDA will continue to refine and expand its inspection system as resources allow.

NEW AND ONGOING ACTIONS TO PROTECT HUMAN RESEARCH SUBJECTS

Overview

Dramatic advances in prevention and treatment of disease have been achieved through research carried out by universities, the private sector and the government. A crucial part of this research involves the voluntary participation of human subjects in clinical trials to test promising but often risky new therapies. Federal policy has sought to preserve the benefits of this research, while at the same time protecting against possible abuse or harm to research subjects. In particular, a regulation implemented by 17 federal agencies, known as the Common Rule, seeks to guarantee review of research for projects and assure willing consent, including a proper understanding of risks involved, for those participating in clinical trials.

The Office for Protection from Research Risks (OPRR) in the Department of Health and Human Services (HHS) is responsible for ensuring the safety and welfare of people who participate in HHS-sponsored research. The Food and Drug Administration (FDA) must approve all clinical trials aimed at testing a new drug, biological product or medical device, and the National Institutes of Health (NIH) has developed important patient safety guidelines that must be followed in any research the agency funds. NIH also has a special panel, the Recombinant DNA Advisory Committee (RAC) that provides oversight and public discussion of gene transfer clinical research.

These agencies work with ethical oversight committees, known as institutional review boards (IRBs), which are responsible for ensuring that people who agree to participate in studies fully understand the nature of the research and willingly consent to participate. This "informed consent" process requires that potential participants be given an explanation of purposes of the research, the expected duration of the subject's participation, a description of the procedures to be followed and their potential risks and benefits, and identification of any procedures that are experimental. Research institutions such as academic health centers and universities have the ultimate responsibility to ensure that clinical investigators adhere to this informed consent process.

In recent years, clinical research has become increasingly complex and has been accompanied by an increase in new ethical and conflict-of-interest considerations. HHS has recognized the need for human subject protections to be strengthened even further, and, as a result, on May 23, 2000 HHS Secretary Donna E. Shalala announced several new efforts designed to improve human research subject safety; to further strengthen government oversight of all medical research, including gene transfer research; and to reinforce clinical researchers' responsibility to follow federal guidelines.

Background

For more than 50 years, HHS agencies have been committed to protecting individuals from possible abuse or harm in clinical trials and to ensuring that prospective and enrolled participants understand the potential risks and potential benefits, if any, of being a research subject. In the 1960s, for example, amendments to the U.S. Food, Drug and Cosmetic Act established requirements that, at a minimum, people must consent to participating in an experimental therapy. A 1967 FDA policy clarified the procedure further to ensure that informed consent be obtained in writing.

In the 1970s, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research furthered protections with recommendations for IRBs, ethical oversight committees that are responsible for ensuring that people who agree to participate in studies fully understand the nature of the research and willingly consent to participate.

In 1972, OPRR was created as part of NIH to ensure the safety and welfare of people who participate in research sponsored by HHS. And in 1981, FDA followed up by revising its regulations to require written informed consent in all studies of products that FDA regulates. Today, FDA, NIH and OPRR continue to play important and complementary roles in overseeing research and protecting the human subjects involved.

Federal Oversight and the IRB Process

OPRR has the primary responsibility within the federal government for developing and implementing the policies, procedures, and regulations to protect human subjects involved in HHS-sponsored research. In carrying out its mission, OPRR has set up formal agreements with more than 4,000 federally-funded universities, hospitals and other medical and behavioral research institutions in the United States and abroad. These agreements or "assurances" outline each institution's commitment to conduct its research projects in an ethically sound manner and to protect the welfare of people involved in these projects.

In accordance with these agreements, each institution sets up one or more IRBs, which are responsible for ensuring that people who agree to participate in studies fully understand the nature of the research and willingly consent to participate. This "informed consent" process requires that potential participants be given an explanation of purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental, among other necessary information.

The membership of an institution's IRB typically includes physicians, scientists, patient representatives and others who are charged with regularly monitoring the design, development and progress of the research projects being conducted at the institution. Federal regulations require that a non-scientist and an individual not affiliated with the institution be included on every IRB.

Guaranteeing Effective Oversight

As the number of research projects and study volunteers increases and clinical research becomes increasingly complex, it is critical that the integrity of research be maintained.

Recognizing the need for further enhancements to existing human subject protections, Secretary Shalala announced on May 23, 2000 several new efforts designed to improve human research subject safety, to further strengthen government oversight of all medical research, and to reinforce clinical researchers' responsibility to follow federal guidelines.

Education and Training. HHS will undertake an aggressive effort to improve the education and training of clinical investigators, IRB members, and associated IRB and institutional staff. NIH, FDA and the Office of Protections from Research Risks (OPRR) will work closely together to ensure that all clinical investigators, research administrators, IRB members and IRB staff receive appropriate research bioethics training and human subjects research training. Such training will be a requirement of all clinical investigators receiving NIH funds and will be a condition of the NIH grant award process and of the OPRR assurance process.

Informed Consent. NIH and FDA will issue specific guidance on informed consent, clarifying that research institutions and sponsors are expected to audit records for evidence of compliance with informed consent requirements. For particularly risky or complex clinical trials, IRBs will be expected to take additional measures, which, for example, could include third-party observation of the informed consent process. The guidance will also reassert the obligation of investigators to reconfirm informed consent of participants upon the occurrence of any significant trial-related event that may affect a subject's willingness to participate in the trial.

Improved Monitoring. NIH will now require investigators conducting smaller-scale early clinical trials (Phase I and Phase II) to submit clinical trial monitoring plans to the NIH at the time of grant application, and will expect investigators to share these plans with IRBs. The NIH already requires investigators to have such plans and they also require large scale (Phase III) trials to have Data and Safety Monitoring Boards (DSMBs). For research on medical products intended to be marketed, FDA will also issue guidelines for DSMBs that will delineate the relationship between DSMBs and IRBs, and define when DSMBs should be required, when they should be independent, their responsibilities, confidentiality issues, operational issues and qualified membership.

Further, OPRR is streamlining its assurance procedures for research institutions. In addition, NIH has issued new guidance allowing grant applicants to defer IRB review of proposed research protocols until after completing the initial phase of NIH peer review but before final funding approval. Previously, NIH asked for IRB review and approval to be documented in all grant applications, even though fewer than half of all applications submitted to NIH are actually funded.

Conflict of Interest. NIH will issue additional guidance to clarify its regulations regarding conflict of interest, which will apply to all NIH-funded research. HHS will also hold public discussions this summer to find new ways to manage conflicts of interest so that research subjects are appropriately informed, and to further ensure that research results are analyzed and presented objectively. In addition, these public discussions also will focus on clarifying and enhancing the informed consent process. Based on these public forums, NIH and FDA will work together to develop new policies for the broader biomedical research community, which will require, for example, that any researchers' financial interest in a clinical trial be disclosed to potential participants.

Civil Monetary Penalties. HHS will pursue legislation to enable FDA to levy civil monetary penalties for violations of informed consent and other important research practices—up to \$250,000 per clinical investigator and up to \$1 million per research institution. While FDA can currently issue warning letters or impose regulatory sanctions that halt research until problems are rectified, financial penalties will give the agency additional tools to sanction research institutions, sponsors and researchers who do not follow federal guidelines. As an interim step, NIH, OPRR and FDA will work more closely together to enforce and target existing penalties.

**HHS Inspector General's Study
Recruiting Human Subjects:
Pressures in Industry-Sponsored Clinical Research
Comments by Sidney M. Wolfe, M.D. and Peter Lurie, M.D., M.P.H.
Public Citizen's Health Research Group**

Somewhat buried in the middle of this highly disturbing report, the authors mention "the transformation of clinical research into a traditional business model." As a result of the shift to this business mindset, the often highly unethical and possibly illegal recruitment practices documented in the Report appear to be increasing rapidly. The rise of separate (from the drug companies themselves) for-profit Human Experimentation Corporations (HECs), a more accurate name for the more benign-sounding name currently in use--Contract Research Organizations (CROs)--has introduced new techniques for rapidly recruiting patients. When combined with the appallingly inadequate Federal regulation of human experimentation in general, and recruitment practices in particular, and the failure (as usual) of the medical profession to police itself, the risk of abuse of patients increases dramatically.

This Report is the first attempt to thoroughly address the issues involved in the recruitment of patients to clinical trials. Most previous writing has been terribly non-specific; this Report is the best available on current practices in this area. However, as good as the Report is in description, it remains weak in prescription. We advocate a much stronger set of recommendations than is provided by the Inspector General's Report; in particular, we advocate promulgating strong new regulations based, in part, on models that are being successfully employed in various settings and which are described in the Report. (See last paragraph of our comments)

More drugs are in clinical trials now than even a few years ago. In addition, many therapeutic categories of drugs, such as those for hypertension, are becoming saturated with drugs, leading to increased competition. More human subjects are therefore needed and the competition to get them approved quickly and beat the competitor drug to the market has intensified. For some drugs, one month earlier to market can mean tens of millions of dollars in additional revenue before the drug is challenged by a generic. Speed and efficiency, from the drug industry's perspective, favor the privatization of human experimentation, moving research away from the academic medical centers where it has traditionally resided. Whereas in 1993, only 20% of pharmaceutical company research was done in the private, for-profit research setting, the fraction has gone up 2 ½ times and by 1998, 50% was being done outside of academic medical centers. The number of private practice-based investigators has grown from 3,153 in 1990 to 11,588 in 1995, an increase of almost four-fold.

According to Richard Friedman of Cornell University in the British journal, the *Lancet*, "In the USA, monetary incentives have spawned a whole industry of private physicians who don't necessarily have any experience in research or with protocols in the specialty areas in which they're testing." These private entities "push patients through trial after trial", with little concern

for what happens to them afterwards. The result is “stop-gap” medicine for vulnerable patients who can't afford treatment any other way, he says. A recent article in the *New York Times* documents how, with 43 million Americans uninsured, many are forced to turn to a series of research studies to remain treated. This invites exploitation.

The Growth of International Research

Drug companies can increase the likelihood of a drug's success by using exclusion criteria to, as one investigator told the Inspector General's office, “enrich trials with patients who are most likely to benefit.” One way to accomplish this is to exclude patients who are currently on medication to treat their condition or even those who have been on medication in the past. Such patients are known in the industry by the double entendre “naive” subjects. These prized subjects are hard to locate but, according to the Report, can often be found among the uninsured or in foreign countries. Many researchers told the Inspector General's staff that drug companies are increasingly looking abroad for such subjects. One advertisement, in this case directed toward possible drug industry customers by the world's largest HEC, North Carolina-based Quintiles--with offices all over the world--promised that they can “even help you tap the vast drug-naive patient populations of China, Korea and other emerging markets.”

The Report points out that the number of new foreign investigators in the FDA's database grew from 988 in the 1990-1992 period to 5,380 in the 1996-1998 period. Aside from easier access to drug-naive patients, the costs for foreign studies are often less than in the United States. Despite this, the FDA only conducted 60 drug investigator inspections abroad in 1998 and, according to the Report, the FDA does not normally inspect foreign Institutional Review Boards (IRBs).

While the Report makes clear that there is increasing internationalization of research, it fails to state that there are ongoing efforts by the research industry to water down the existing international ethics documents to facilitate some of the practices the Report finds troubling. The current version of the Declaration of Helsinki states that, if the patient has a dependent relationship with the investigator, “the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.” (It is noteworthy, as the Report documents, how widely this international ethics document is ignored.) Some have proposed that this language be replaced by the following: “In some cases of this type, it may be preferable if the informed consent were to be obtained by a qualified person who is not engaged in the investigation, independent of the dependent relationship, or both.” This is precisely the wrong direction for changes in ethical practice at a time when pressures to recruit are increasing.

Recruitment Method Concerns

The four main categories of findings in the Report which we believe demand action are:

Offering Incentives

Because human experimentation has been transformed to a “business model”, this newly emerging “business” of experimenting on people has every imaginable incentive for fast recruitment and fast results. A bonus of \$30,000 after recruiting the first six patients and a bonus of \$6000 per additional patient captures the “competitive enrollment” which, according to the Report, “encourages aggressive recruiting.”

Targeting Own Patients

In concordance with a *New York Times* investigation documenting doctors getting paid as much as several thousand dollars per patient to recruit patients from their own practices, the policy of recruitment by physicians of patients from their own practices is further documented in the Report. The vulnerability of a doctor’s own patients to be persuaded to become an experimental research subject because of their trust in their doctor, combined with signing bonuses which the doctor pockets for the referral sets up a toxic situation where some doctors are literally selling their own patients into human experiments. In a gross commercialization of this practice, one large family practice group advertised its “computerized patient data base of 40,000 patients” to HECs and others running clinical trials as one from which “We can actively recruit patients for any study...”

Seeking Additional Patient Bases

In addition to plumbing their own files for potential experimental subjects, some researchers pay “finder’s fees” to other doctors who do not even conduct the research: “Occasionally, investigators offer fees to encourage referrals from other physicians or nurses,” such as an offer of \$75 to physicians or nurses for each subject referred, according to the Report. The use of patients reached through patient advocacy groups, also described in the Report, similarly has the taint of using a relationship of trust to recruit patients who might otherwise not be interested in participation in such experiments.

Advertising and Promotion

The “new industry of patient recruitment firms and research marketing companies” has produced, according to the Report, more advertising for human subjects than in the past. Until public criticism changed this practice, the website DrKOOP.com was using the formerly good name of this medical huckster to recruit patients, for a finder’s fee, to the multinational HEC Quintiles.

Erosion of Informed Consent

The Report expresses serious concern about the way the business model of research, as manifested through the practices described above, might erode the essential elements of informed consent.

Information: The Report describes misleading advertisements which blurred the distinction between treatment and research, an excessive focus on monetary or other compensation which can become coercive and the lack of response by drug sponsors to concerns raised by IRBs in the less-than-frequent instances in which the IRBs actually review the advertisements.

Comprehension: The failure to conduct research on or to audit the extent that the patient actually understands the recruitment materials and the informed consent forms is of concern. According to the report, the performance of the physician/investigator in fully informing patients may be compromised by bonuses for more patients recruited and by promises of top authorship on papers emanating from the research tied to recruiting success.

Voluntariness: One medical journal article concerning effective human subject recruitment strategies noted that “Done correctly, [media] publicity can look like an endorsement by your well-respected newspaper reporter or TV news anchor. It can be an excellent way to generate phone calls needed to fill studies.” This part of the Report reiterates the concerns about doctors recruiting patients from their own practices and states that “patients see their doctor as God” because of the trust they place in them.

Successful Models

While the Inspector General’s Report makes clear that there is little in the way of guidelines or regulations to prevent the kinds of abuses the Report documents, it does contain a number of examples of innovative approaches that the Report should endorse, rather than merely mention. These fall into the categories of recruitment incentives, the dual physician-investigator role and confidentiality of medical records. Unfortunately, the Report merely identifies four questions that need to be addressed (page 31 of the current draft), rather than recommending the answers that the Report’s evidence would seem to require and which these models prove is feasible.

Several groups (University of Rochester IRB, Partners HealthCare System) have banned the use of bonus payments designed to encourage patient recruitment, while Partners HealthCare System and the American Medical Association also ban fees for referring patients to other investigators, HECs or drug companies. We strongly endorse these initiatives. We believe that physicians have a right to reasonable reimbursement for any costs incurred or time spent beyond what they would ordinarily expend in the care of the patient, but no more. We agree in general with efforts to increase disclosure of potentially conflicting interests to patients. But we are opposed to using disclosure of such interests as a substitute for banning the more egregious of

these incentives.

Disclosure has also been the preferred approach (when any approach is put forth) by universities (University of California at Los Angeles) to the problem of the dual physician-investigator role. However, some groups have stated that, at least in some circumstances, the preferred approach is to have a more neutral intermediary, without the conflict of interest of the investigator approaching the patient. We believe that this approach should be more the norm than the exception. As is almost always the case, the preferred method for resolving potential conflicts of interest is to involve neutral third parties.

Finally, the Report makes clear how little work has been done, particularly by medical associations, in addressing the problem of researchers using databases that include patients cared for by another health care provider to recruit study participants. This is an improper invasion of privacy and is precluded by some IRBs (Medical College of Ohio, University of California Los Angeles, Partners HealthCare System). All IRBs should follow this model.

In sum, the Report has clearly identified a wide range of relatively new threats to patients in clinical research studies. Furthermore, this burgeoning field is largely unregulated. Even when the IRBs have particular authority, they appear unwilling or unable to exercise their authority. And some of the Report's solutions are to give more authority to IRBs, which the Inspector General's previous reports have already documented are hopelessly overworked. The following are appropriate subjects for regulation: banning finder's fees; banning reimbursement to physicians beyond research-related expenses and time expended; mandatory disclosure to the potential participant of the source and amount of all recruitment fees; and restrictions on the ability of health care providers other than the patient's physician from gaining access to a patient's medical records for the purpose of recruitment. In the absence of regulation, therefore, sponsors will be able to choose the route least protective of patients' rights in their quest to maximize recruitment--the ethical "race to the bottom" of which the Report warns and which has characterized much of globalization to date.

Bert Spilker, PhD, MD
 SENIOR VICE PRESIDENT
 SCIENTIFIC AND REGULATORY AFFAIRS



April 12, 2000

June Gibbs Brown
 Inspector General
 Office of Inspector General
 Room 5250 Cohen Building
 330 Independence Avenue, S.W.
 Washington, DC 20201

Re: Comments on the Draft HHS-OIG Reports: Recruiting Human
 Subjects OEI-01-97-00195 and 00196.

Dear Dr. Gibbs:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing more than \$26 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

We appreciate your sending a copy of the above noted draft reports to Mr. Alan Holmer on March 10, 2000 for our comments. Our comments are limited to Report 00195.

The pharmaceutical industry agrees with the stated overall goal: to achieve a level playing field in the area of recruitment.

We are concerned that the report is anecdotal and contains a number of false or overly simplistic statements. And overall, it displays a certain degree of naiveté about the subject being discussed. Despite these limitations, the Report is reasonably well-written and fairly balanced, and contains many appropriate observations.

This Report expresses concern about a number of practices that we wish to comment on:

Pharmaceutical Research and Manufacturers of America

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- **Targeting patients in the investigator's own practice.** The Report expresses concern that the inherent duality of interest may cause the investigator not to act in the best interest of the patient. In particular, the Report expresses concern that the relationship between the investigator and the Sponsor are not disclosed to a patient. *Comment: As required by FDA regulations, the research nature of this relationship should be disclosed in informed consent forms. Investigators who recruit their own patients especially should ensure that patients understand the investigator's role.*
- **Seeking referrals from the investigator's colleagues and dissemination of study information to patient support or disease advocacy groups.** The Report expresses concern about compromised confidentiality if patient databases are searched for specific diagnoses in order to identify prospective subjects. *Comment: Access to patient databases is a key factor in the identification of potential study subjects, especially by CROs. Any limitations to this access should be addressed by appropriate IRBs. However, permission from prospective subjects should be sought if databases are to be maintained for the purpose of third party access to identify potential research subjects. To protect confidentiality, access to patient medical records should be limited to the physician or designee(s) at a specific site.*
- **Aggressive advertising and promotion through the media, press releases, or speaking engagements.** The report expresses concern that the key components of informed consent, information, comprehension and voluntariness, may be compromised by incomplete or misleading advertising. *Comment: As is the current practice, IRBs should review and approve any form of direct patient contact related to research studies, including advertising.*
- **Aggressive follow-up from study sponsors, including phone calls and the use of newsletters.** The Report expresses concern that these methods may compromise the objectivity of investigators and study coordinators. *Comment: Frequent contact with study sites is important to successful study enrollment. However, this form of contact should not compromise the objectivity of study personnel in identifying, obtaining informed consent from, and enrolling appropriate study subjects.*

Specific Comments

Page 11, second paragraph - "The clock for a drug patent starts running at the beginning of the clinical testing phase." This is false. The patent clock used to start in the U.S. when the patent was issued. As is the international norm, it now starts when the patent application is filed.

Page 11, third paragraph - While this paragraph implies that newsletters with enrollment charts are a questionable practice - it is usually viewed by investigators and sponsors as an efficient way to keep the lines of communication open between the sponsor and study sites. It keeps a trial in people's minds, which is a real challenge for a year (or longer) trial.

Page 11, last sentence and on page 12 top - This requirement may be mandated by FDA. It is also related to the needs of Phase II trials for a narrow homogeneous population.

Page 12, 1st paragraph, last sentence - While the investigator's comment was meant to be negative, isn't the purpose of a new drug to help more patients? Did the patients meet inclusion criteria? Was the trial controlled? Those are the key questions to address in deciding whether patients enrolled are appropriate.

Page 12, paragraph 2 - The FDA often desires or even insists that sponsors find and enroll drug-naïve patients.

Many statements imply that sponsors themselves are making many decisions on recruitment, whereas in fact many such decisions are actually made with FDA staff, or by FDA staff themselves. The next paragraph on page 12 also omits including the influence of the FDA.

The desire (or need) of a sponsor for a global launch of a new drug is also omitted in paragraph 3.

Page 12, second paragraph from bottom - This omits discussing the changing responsibility for patient recruitment from investigators to sponsors and their vendors (e.g., CROs, recruitment companies).

Page 13, last paragraph, lines 6-8 - Sponsors must ask these questions (and often request evidence to support the investigators' statements) at the first site visit in order to assess the appropriateness of the site, and not after a contract is signed.

Page 13, last paragraph, last 5 lines - The draft Report questions these practices without acknowledging the other side of the argument -- that investigators make gross overestimates of their ability to enroll patients. I would suggest that you mention this practice as well, as it raises various ethical issues.

Page 25, Table - Can you add the correct answers to the questions posed, possibly as a footnote?

Page 27, first three lines of last paragraph - Monitors generally visit sites about every 6 weeks, and are primarily responsible for assuring the integrity of the data. While monitors generally have no direct patient contact, to the extent possible, monitors are attuned to issues of patient protection and attempt to identify potential issues.

The statement that “sponsors are ultimately responsible for ongoing safety of subjects” because of our monitoring responsibilities is misleading. In fact, 21 CFR 312.60 states that investigators are responsible for “protecting the rights, safety, and welfare of the subjects under the investigator’s care.” We certainly do not disclaim responsibility to support patient safety, but it should be pointed out that the investigator is directly responsible, and that sponsors can provide support in many different ways. Adding this context would address the point being made on page 27 that the activities of monitors are supportive, but not sufficient, to protect patients.

Overall, it is disappointing that this Report does not proactively discuss the creation and use of practical recruitment strategies.

Other assertions of the Report:

Provide IRBs With Authority to Oversee Recruitment. They already have this role. The Report cites a few general regulations and guidances in support of providing IRBs with clear authority to oversee recruitment, but may have it overlooked the most direct source: 21 CFR 56.111 requires IRBs to ensure that the “selection of subjects is equitable.” This is usually read to include the process of selecting subjects in addition to the substantive eligibility criteria.

Facilitate Development of Guidelines. The Report recommends industry involvement in this process of developing guidance. We concur with this, and would be enthusiastic to participate.

Ensure Adequate Education of Investigators and IRBs. We agree with the need to continue to educate these parties, but disagree with a formal “one-size-fit-all” requirement as may be suggested as a prerequisite for physicians to act as investigators. The report states that awareness of these issues and educational opportunities are on the rise – we should all support that trend by participating in and, when feasible, sponsoring education, and (for the sponsor’s part) emphasizing the issue when we select and train investigators (e.g., at start-up meetings).

Strengthen Federal Oversight over IRBs. If this strengthens the IRB process, it should help all parties involved.

The Report gives an inadequate description of the sponsor processes that are in place to address the potential concerns raised by the recruiting pressures on investigators. The Report should at least acknowledge that protocols typically contain detailed inclusion/exclusion criteria, that physicians are trained on interpreting these criteria at start-up meetings, that one or more of the sponsor's physicians are in charge of overseeing the implementation of these criteria by investigators and often answer such questions, that monitors check adherence to these criteria, and that subjects who are enrolled outside of these criteria may be discontinued from the study. There are also requirements for sponsor approval of informed consent documents that allows sponsors to support patient protection in the areas of consent and confidentiality.

Page 32, 3a and 3b - Does not contain comments on how this would, can, or should be achieved. This is an unfortunate omission.

A final suggestion is in the basic organization of the Report. The Report mentions several times that there are "four main 'recruitment strategies'" used by sponsors and investigators. In fact, what is listed are three "sources" of patients (i.e., the investigator's own patients, or patients that are referred by another physician or contacted through advertising). Again, I think it's misleading to call these three "recruitment strategies", when they are the only inherent processes by which patients may come in contact with the investigators. The fourth category - "offering incentives" - is not a source of patients. Rather, it describes the inducements that are either inherent in the process or offered by the sponsor related to patient enrollment.

Thank you very much for allowing us the opportunity to comment on this Report.

Sincerely,



Bert A. Spilker, PhD, MD

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Joan Rachlin, J.D., M.P.H., Executive Director

April 20, 2000

Mark R. Yessian, Ph.D.
Regional Inspector General for Evaluation and Inspections
Dept. of Health & Human Services
JFK Federal Bldg., Room 2225
Boston, MA 02206

Dear Dr. Yessian:

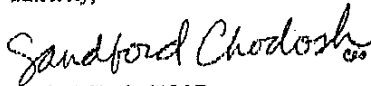
In response to your kind offer to take an "early look" at your report on recruiting human subjects for clinical research, please find attached the comments of Applied Research Ethics National Association (ARENA), our affiliate organization. We support without reservation the content of ARENA's letter, and urge you to consider the points therein.

We would like you to consider expanding the reach of the Report's "grasp" to include the additional forms of IRBs, including, but not limited to, central and independent IRBs, as well as the variety of organizations that fund research and ultimately propose the range of recruitment practices covered in the Report. More specifically, IRBs can only review the recruitment practices that are provided to them.

As mentioned above, because there are a variety of types of IRBs (institutional, central, e.g., the cooperative oncology groups, and independent IRBs), I would respectfully request that the OIG Report comment on the resultant differences in the types of recruitment practices depending on the source of funding, and/or the type of IRB performing the review. There are, I maintain, differences among them, and the different "cultures" in which the research takes place will necessarily affect the nature of, and response to, proffered corrective actions.

In general, it is my hope that this Report will function as a "wake up call" for those who create and promulgate questionable, or patently unethical recruitment practices, and I am therefore grateful for your efforts to bring some of the problems with subject recruitment to light.

Sincerely,



Sanford Chodos, M.D.
President, PRIM&R

JR/cs

cc: Susan Kornetsky, President, ARENA
Ada Sue Selwitz, Chair, ARENA Public Policy Committee



April 20, 2000

June Gibbs Brown
 Inspector General
 Department of Health and Human Services
 Washington, DC 20201

Dear Ms. Gibbs Brown:

Thank you for providing ARENA with the opportunity to review and comment on the two draft reports on recruiting human subjects for clinical research (OEI-01-97-00195 and OEI-01-97-00196). Applied Research Ethics National Association (ARENA) is a subsidiary of Public Responsibility in Medicine and Research (PRIM&R), a nonprofit organization dedicated to promoting the ethical conduct of research. ARENA is a professional association with 900 members who are administrators, chairs, and members of Institutional Review Boards (IRBs) and Institutional Animal Care and Use Committees (IACUCs) throughout the United States. ARENA's mission is to support those professionals whose responsibilities include the protection of human and animal research subjects.

We wish to commend you for beginning the exploration of this difficult area and for initiating a dialogue on problems and solutions. The Report entitled, "Sample Guidelines for Practice" provides useful examples and guidance that can be considered in recruiting practices. ARENA fully agrees with this guidance and has no further comment on this Report.

ARENA finds the main Report to be timely, thoughtful, and useful. The Report highlights recruitment issues that IRBs are concerned about, including conflicts of interest and large subject payments. This Report gives credibility to the recruitment issues that IRBs, sponsors, federal agencies, and investigators need to consider and resolve. We hope that the Report will give "clout" and "enhanced substantive grounds" to IRBs that question recruitment practices. Also, the Report may function as a "wake up call" for those who create and promulgate questionable, or patently unethical recruitment practices, and we are therefore grateful for your efforts to bring some of the problems with subject recruitment to light.

Although we applaud the efforts of the Office of Inspector General (herein after "OIG"), ARENA offers the following three general comments:

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First, that the Report focuses too heavily on IRBs and misdirects attention away from the constituencies that actually initiate and control recruitment practices. The Institutional Review Board system is only one part of the picture; recommendations need to be directed to other constituencies as well. In fact, IRBs have tried to address and solve many of the issues raised in your Report. However, to be effective, IRBs need the support and cooperation of the federal and other regulatory agencies, as well as the sponsors and investigators, in order for meaningful changes to be made. Focusing six of the eight recommendations on IRBs gives the impression that that the problems and their repair are solely the province of IRBs, when in fact other constituencies such as sponsors, investigators, and regulators also need to address specific issues. Protection of human subjects is a shared responsibility. We feel that the Report should more explicitly acknowledge that IRBs are not the sole – or even primary – source of the problem.

Second, IRBs review the recruitment practices that are developed by either individual investigators or sponsors. There are a variety of organizations that fund research and propose the respective recruitment practices. The Report does not comment on whether there are differences in the types of recruitment practices depending on the source of funding. If there are differences, these factors may be important, since subsequent corrective actions could be focused on where the problems initially occur.

Third, in the June 1998, Report, the OIG acknowledged that IRBs are under-resourced and overworked. Although ARENA supports efforts to promote ethical recruitment procedures, we also are sensitive to fiscal and practical realities which impact IRBs' abilities to achieve this goal. Throughout the Report, there are recommendations which have the potential to increase workload and/or costs (e.g. mandatory training). This is a challenging issue, one that cannot be resolved easily. The OIG needs to support efforts to impede erosion of Facilities and Administration costs (i.e. indirect costs), and make recommendations for other avenues of funding.

In addition to these three general comments, below are five more specific comments:

- a) In the "Executive Summary Findings," the Report comments, "recent investigations and complaints reveal disturbing recruitment practices," and follows with three examples. While these practices undoubtedly did occur, they constitute a small percentage of subject recruitment, compared to the thousands of clinical trials that have used appropriate recruiting procedures. It may be helpful to acknowledge that these are extreme examples, and to further acknowledge that unacceptable recruitment practices can and will continue at an increasing rate if unethical recruitment practices are not addressed.
- b) In the discussion on the "Quest for Efficient Research Sites," the Report indicates that the growing numbers of first-time investigators who have not been trained in clinical research may contribute to the use of questionable practices. ARENA agrees with this observation, and suggests that this "change" should be added to the table on "Changing Clinical Trials Environment" (refer to page 10).

The only recommendation that addresses first-time investigator training is 3a. While the call for education is an excellent first step, mentoring, monitoring, and progressive responsibility are additional areas ripe for recommendation. More attention should be focused on this issue.

c) The section subheading, "IRBs are not reviewing many of the recruitment practices that they and others find most troubling" may be misleading. Recruitment incentives are a small, albeit ethically sensitive, portion of the financial arrangements between sponsors and investigators. Within the IRB community there are different practices for reviewing financial arrangements in addition to payment to subjects. ARENA agrees that individuals and institutions should have appropriate mechanisms in place to consider and address these difficult issues, and to prevent unacceptable financial and recruitment practices. Other issues, such as investigator conflicts of interest and inappropriate pressure generated by sponsors, also need to be brought into the equation. This can be done in a number of different ways. For example, in some institutions, the IRB may fulfill this role by reviewing all financial arrangements. In other institutions, offices of sponsored programs or clinical trials share in this responsibility. Acceptable practices need to be established and a mechanism for review and adherence to these practices must be put into place. This is not solely an IRB responsibility.

d) The Report suggests that FDA and OPRR should develop questions that IRBs can ask when reviewing recruitment materials and processes. These agencies should be cautious when developing guidance, and we respectfully recommend that they be asked to seek input from experts in the IRB field. Interpretation of the questions will be essential, and involvement of the IRBs in the development stage may prevent misunderstandings or misguided questions. Also, when agencies develop "questions", those guidelines are often translated into "regulation" which must be applied and documented for each review. It would be helpful to have OPRR and FDA suggest concepts and give examples of acceptable practices, and to then permit the institutions to find the approaches which best meet their needs.

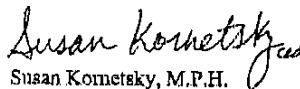
e) Recommendation 2 is addressed to the federal regulators. This recommendation could offer valuable assistance, especially if the wider issues described above and contained elsewhere in the Report are addressed. A national dialogue would be an important step in arriving at acceptable solutions and practices. Such a step would be extremely valuable if everyone (sponsors, professional organizations, investigators, IRBs, and regulators) is provided with guiding principles to be used in considering recruitment practices.

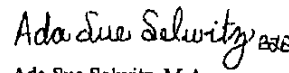
f) The registration for IRBs called for in recommendation 4a needs to be given careful thought. Registration will provide a vehicle for improved communication and education, however, it is not clear that, in and of itself, it will solve recruitment issues raised by the Report. Registration processes can vary from the


simple name and address format to a complicated and detailed descriptive mechanism. The federal implementation of the Report's suggestion of submitting "brief descriptive information" is worrisome, since this may become yet another burden for IRBs.

In conclusion, ARENA agrees that ensuring essential human subject protection without unnecessarily hindering research is a critical challenge. The Report brings into focus important issues. ARENA thanks you for the opportunity to provide our comments. We look forward to providing additional comments or other assistance, as your office continues to address these and other dimensions of protecting those who participate in biomedical and behavioral research.

Sincerely,


Susan Kornetsky, M.P.H.
ARENA President


Ada Sue Selwitz, M.A.
ARENA Public Policy Committee Co-Chair


Gary Chadwick, Pharm.D., M.P.H.
ARENA Immediate Past-President

cc: Erica Heath, ARENA Drafting Subcommittee
Elizabeth Bankert, ARENA Drafting Subcommittee
Karen Hansen, ARENA Drafting Subcommittee
Peter Marshall, ARENA Drafting Subcommittee

Sanford Chodosh, President, PRIM&R
Joan Rachlin, Executive Director, PRIM&R

**CONSORTIUM OF
INDEPENDENT
REVIEW BOARDS**

CIRB **CIRB**

April 13, 2000

June Gibbs Brown
Inspector General
Office of Inspector General
Department of Health and Human Service
330 Independence Avenue, S.W.
Washington, D.C. 20201

Re: Draft Reports Concerning Recruiting of Human Subjects

Dear Ms. Brown:

On behalf of the Consortium of Independent Review Boards ("CIRB"), we applaud the Department of Health and Human Services' ("HHS") Office of Inspector General ("OIG") on its draft report and sample guidelines for practice concerning recruitment of human subjects for clinical trials. CIRB heartily supports OIG's review of the clinical research recruitment process and generally endorses its recommendations. However, CIRB has several comments that it believes will strengthen these drafts and clarify the OIG's recommendations. Provided below are our comments concerning the following draft documents: (1) *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research* (Draft Report); and (2) *Recruiting Human Subjects: Sample Guidelines for Practice* (Sample Guidelines). The CIRB membership hopes that its comments will be helpful to OIG as it finalizes these draft documents.

I. Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research

As stated above, CIRB generally supports the OIG's discussion of the human subject recruitment process. However, it has several observations. First, CIRB believes that the subtitle of the Draft Report, *Pressures in Industry-Sponsored Clinical Research*, as well as several statements within the Draft Report itself, fail to recognize fully the extent of the OIG's review of the recruitment process. The Draft Report demonstrates a review of patient recruitment issues associated with both federally-funded research and industry-sponsored research. CIRB agrees that the use of recruitment incentive offers and the "rush to market" mentality is unique to research supported by industry sponsors. However, all other recruitment strategies and pressures

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identified in this report are employed in both the federally-funded research setting and the industry-sponsored research setting. Indeed, OIG's discussion of a study in which patients were recontacted by investigators numerous times in an effort to persuade them to enroll (page 2 of Draft Report) reminds CIRB of facts leading up to the Office of Protection from Research Risk's ("OPRR") recent suspension of an Assurance Agreement with an institution conducting a federally-funded study of the causes of Alzheimer's disease. Thus, as this report makes clear, the pressures on clinical investigators conducting federally-funded research (e.g., university pressures associated with tenure, grant priority) also can result in questionable human subject recruitment practices.

Further, as we are sure OIG understands, while many institutions may conduct both industry-sponsored research and federally-funded research, OPRR's jurisdiction is limited to federally-funded studies. Thus, OIG's discussion of OPRR's enforcement measures in connection with industry-sponsored research is arguably misplaced. We would suggest that in order to fully encompass the true scope of OIG's extensive review of the human subject recruitment process, OIG revise the Draft Report title and the Draft Report content to recognize that its comments are of significance to both federally-funded research and industry-sponsored research by titling it *Pressures Used in Recruiting Human Subjects*.

CIRB's second comment concerns the absence of a discussion of FDA's oversight function under the subsection entitled "Oversight of the recruitment of human subjects is minimal and largely unresponsive to emerging concerns." See Page 3 of Draft Report. CIRB believes that the Draft Report should briefly discuss FDA's oversight authority in this area. Further, CIRB brings to OIG's attention FDA's Guidance for Institutional Review Boards and Clinical Investigators, which contains an Information Sheet specifically entitled "Recruiting Study Subjects."

CIRB also notes the absence of a discussion of IRBs, FDA, and OPRR in the section of the Draft Report entitled, *The Main Players in Clinical Trials*. See Page 9 of Draft Report. This section is intended to describe the many parties who play a role in the conduct of clinical trials. Clearly IRBs, FDA, and the OPRR play significant roles in this process and CIRB believes mention of those roles should be identified. For example, an industry-sponsor generally must submit an Investigational New Drug ("IND") application to FDA prior to commencing clinical research. Among other things, the FDA reviews these applications to assure the safety and rights of human subjects. 21 C.F.R. § 312.22. FDA can order a clinical hold (an order to delay commencing a study or to suspend an ongoing investigation) if it believes the safety or rights of subjects are not sufficiently protected. 21 C.F.R. § 312.42. Further, industry-sponsors frequently meet with FDA prior to commencing a clinical study or while the study is ongoing to apprise FDA about the study and to obtain information from FDA as to what it expects for purposes of approval of a New Drug Application. 21 C.F.R. § 312.47. Among other things, these meetings provide FDA with the opportunity to question the number of subjects in a protocol, the exclusion and inclusion criteria, and the study design itself. It is not unusual for sponsors to completely redesign a study design to address FDA's questions. FDA may require

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more studies or more subjects. Thus FDA can have a significant role in driving the search for more subjects that meet tighter eligibility criteria.

With regard to OIG's discussion of health professional referral fees on pages 16 and 17 of the Draft Report under the subtitle, *Seeking Additional Patient Bases*, CIRB wishes to bring to OIG's attention that, at least in some states, it is against the law to pay referral fees to health professionals for referring patients for enrollment in clinical research.

In paragraph three of the introduction to the Draft Report Recommendation section, OIG states "As we have shown in a previous report, they review too much, too quickly, with too little expertise." See Page 29 of Draft Report. It is CIRB's understanding that this statement refers to OIG's June 1998 report entitled *Institutional Review Boards: A Time for Reform* ("June 1998 Report"). The June 1998 Report also identified insufficient resources as a problem for many IRBs. Thus, CIRB recommends extending this statement by adding "... and too few resources."

CIRB's strongest endorsement concerns OIG's recommendation that FDA and OPRR provide guidance regarding the IRB's authority to review recruiting material. As the Draft Report adequately reflects, outside the advertising and promotion context, most IRBs are unsure about their authority to review recruiting practices such as investigator's selection of or pursuit of an adequate patient base. Further, CIRB also believes that clinical investigators and sponsors require direction regarding appropriate human subject recruitment practices. Therefore, CIRB fully believes that it is absolutely critical that FDA and OPRR issue guidance documents that clearly specify appropriate human subject recruitment practices and the measures IRBs must take to fulfill their responsibility to adequately review such practices.

Because the solution to the problems associated with human subject recruitment can only be addressed by collaboration among all parties involved in clinical research, CIRB believes these guidance documents should be directed not only to IRBs, but to sponsors and clinical investigators as well. Therefore, it suggests revising the titles for Recommendation 1 and Recommendation 1b to read as follows: *Provide IRBs, Sponsors, and Clinical Investigators with direction regarding appropriate recruitment practices.*

CIRB has always supported OIG's recommendation regarding investigators and IRB board member training on human subject protections, as well as its recommendation regarding IRB registration requirements. Finally, while CIRB is not averse to requiring more extensive representation of nonscientific and noninstitutional members on IRBs, CIRB believes that there has been no research to suggest that a larger IRB will benefit human protection. While some studies may benefit from a review by a Board composed of a greater number of nonscientific members, other studies may require a more scientifically-based Board that can fully understand the science behind the study in order to analyze the risks to human subjects. Therefore, CIRB is concerned that an increase in size or representation alone may not be beneficial.

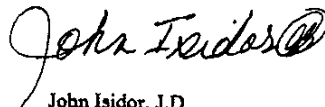
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2. Recruiting Human Subjects: Sample Guidelines for Practice

CIRB believes that the Sample Guidelines are an excellent starting point in the discussion that will be necessary to determine appropriate recruitment practices and measures to ensure that only appropriate practices are followed. However, CIRB provides one observation regarding OIG's interpretation of certain professional medical associations statements in the context of patient recruitment for clinical studies. While some professional associations have set forth ethical guidelines that relate specifically to research, other associations have general guidelines that OIG has extrapolated to support its recommendations regarding appropriate recruitment practices. While CIRB has not reviewed all documents referenced by OIG, it is concerned that the extrapolation of general medical practice guidelines to research may not be appropriate or in the best interest of the patient. We are of the view that the creation of guidelines would no doubt address what is necessary to protect human subjects.

Again, we extend our congratulations on the report and thank you for the opportunity to comment on these draft documents. We hope that the OIG will feel free to contact CIRB if we can be of any assistance.

Sincerely,



John Isidor, J.D.
Chairman

AMB/amb

cc: CIRB Membership
Mr. George Grob, OIG
Dr. Mark Yessian, OIG

Endnotes

1. Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: A Time For Reform*, OEI-01-97-00193, June 1998.
 2. Niblack, J.F. “Why are Drug Development Programs Growing in Size and Cost? A View from Industry,” *Food and Drug Law Journal* 1997; 52: 151-154.
 3. Association of Clinical Research Professionals, *ACRP’s White Paper on Future Trends*, Spring 1999, p.3.
 4. In 1990, total (domestic and foreign) drug research and development expenditures was \$8.4 billion. This number rose to an estimated \$24 billion in 1999. Pharmaceutical Research and Manufacturers of America, *PhRMA Industry Profile 1999*, Chapter 2, p. 15.
 5. Miller, K.L. and Pryce, S.L. “Better, Faster, Worldwide Too— Update on Pharmaceutical Contract Support Organizations,” a Hambrecht & Quist, L.L.C., Industry Report, Jan. 4, 1999.
 6. For example, in 1995, the average number of clinical and outcome procedures per protocol was 189, up from an average of 100 in 1991. From DataEdge, 1995 as cited in *PAREXEL’s Pharmaceutical R&D Statistical Sourcebook*, 1998: p.51.
- Trials are becoming more complex as they attempt to provide information to more “customers”. According to Niblack, these customers include, but are not limited to, the sponsor’s business management and shareholders, both national and international government regulators, opinion leaders in academic medicine, practicing physicians, formulary managers, and patients and their families. Each of these customers are seeking different types of information that can only be ascertained by adding more procedures or more subjects to a trial.
- Niblack, JF. “Why are Drug Development Programs Growing in Size and Cost? A View from Industry,” *Food and Drug Law Journal* 1997; 52: 151-154.
7. Pharmaceutical Research and Manufacturers of America, *PhRMA Industry Profile 1998*, Chapter 3, p. 27.
 8. Association of Clinical Research Professionals, *ACRP’s White Paper on Future Trends: Faster Time to Market*, 1998, p.10.
 9. Hovde, M. and Seskin, R. “Selecting U.S. Clinical Investigators,” *Applied Clinical Trials* 1997: p. 35.

10. Association of Clinical Research Professionals, “Sponsor Strategies To Reduce Development Costs and Cycle Times,” *ACRP White Paper Part 2*, 1997, p. 5.

Another indication of the inexperience of investigators is that, according to our analysis of the FDA investigational new drug database, 58 percent of investigators listed in it have only conducted one trial between 1980-98.

11. Association of Clinical Research Professionals, “Sponsor Strategies To Reduce Development Costs and Cycle Times,” *ACRP White Paper Part 2*, 1997, p. 8.

12. Poor enrollment has been blamed for 25 percent of delays in drug development. Harper, B and Moench, L. “Emerging Patient Recruitment Performance and Cost Metrics” in *PAREXEL’s Pharmaceutical R&D Statistical Sourcebook*, 1998: p. 57.

13. Nearly 78 percent of clinical trials miss enrollment deadlines established by the sponsors. Ibid.

14. The drug industry estimates that “in order to sustain corporate earnings and Wall Street expectations, [pharmaceutical industry] output must be doubled in order to meet this ‘minimum hurdle.’ Moving beyond this requires a tripling of output.”

Association of Clinical Research Professionals, *ACRP’s White Paper on Future Trends: Faster Time to Market*, 1998, p.5.

15. DataEdge gives an example of a real case study in which a database with 1.8 million patients was queried to find the numbers that meet a particular protocol’s eligibility criteria. The query revealed that 9,700 patients had the condition called for in the protocol, yet only 581 met all of the 18 eligibility criteria (or .03 percent). See DataEdge, “Patient Treatment Data: the Hidden Key to Faster Studies,” pg. 3. [<http://www.dataedge.com/La1297.html>, accessed Sept. 1999]

In cancer trials, “the largest single reason for the very low proportion of patients who are enrolled in clinical trials ...is eligibility rather than patient...refusal to enroll.”

Freedman, B. “Multicenter Trials and Subject Eligibility: Should Local IRBs Play a Role?” *IRB* 1994;16(1):2.

16. Langreth, R. “Drug Marketing Drives Many Clinical Trials,” *The Wall Street Journal*, 16 November 1998, A10.

17. Kaitlin, K. “Global Drug Development and International Harmonization: the Emergence of China as a World Pharmaceutical Player,” *Drug Information Journal* 1998; 32: 1187S.

18. The termination in June 1999 of the Clinical Research and Investigator Services (CRIS) portion of the University Health System Consortium, a consortium of 35 major academic research centers, is evidence of academic health centers’ struggle to compete with non-academic sites. CRIS was created to help academic centers compete with other research sites for industry-sponsored research. However, according to a recent *Centerwatch* article, “it was determined that

the clinical trials market was too competitive and changing too quickly for UHC to keep pace. “UHC Closes Its Doors to Clinical Research,” *Centerwatch* 1999;6(8):8.

19. A. Miller, “Trial Run,” *American Medical News*, 27 September 1999; 42(36):17. Also, Harris, S.M. “Issues to Consider in Clinical Trial Agreements,” *American Medical News*, 27 March 2000; 43(12):17.

20. A 1996 survey of 55 investigative sites found that the average research contract dropped from \$50,000 in 1994 to \$43,000 in 1996.

Association of Clinical Research Professionals, “Sponsor Strategies To Reduce Development Costs and Cycle Times,” *ACRP White Paper Part 2* 1997; p. 5.

Also see “AMC Models for Reform,” *Centerwatch* 1997; 4(7):1 and “Bonuses to the Rescue,” *Centerwatch* 1998; (5)11:1.

21. For each trial, sponsors and investigators may use any combination of the available methods and the methods are chosen based on the type of trial, the target population, and available resources.

22. According to one recruitment specialist, this method encourages sites to compete with one another rather than working collaboratively to establish effective recruitment strategies.

23. In a survey of 35 sites, the percentage of their contracts that included subject recruitment bonuses increased from 14 percent in 1996 to 21 percent in 1998. “Bonuses to the Rescue,” *Centerwatch* 1998; 5(11):1.

24. Glass, H.E. “Higher Payments to Investigators Don’t Speed Study Completion,” *Applied Clinical Trials* 1995; 4:40-48. Also in Harper, B.S. “The Effectiveness of Sponsor/CRO-Site Performance Incentives,” *The Monitor* 1997; [<http://www.acrpnet.org/monitor/fall97/html/article1.html>, accessed Nov. 1998].

25. We also heard that sponsors are beginning to analyze prescribing patterns in order to identify physicians for a study. Prescribing patterns can help to identify physicians with a large number of patients with a certain ailment and, in turn, areas of market potential (i.e., physicians that are prescribing a competitor’s drug).

26. The combined power of a group of independent physicians, and hence patient databases, have made site management organizations (SMOs) a new force in the clinical trials arena.

27. The reluctance of physicians to refer patients into research trials is problematic not only because it can lead to a dearth of subjects, but also because it can be a source of selection bias. See Dicker, B. and Kent, D. “Physician Consent and Researchers’ Access to Patients,” *Epidemiology* 1990; 1(2): 160-3.

28. The researchers who found referrals a valuable source of subjects were those whose research focused on terminal or life-threatening conditions, such as cancer or AIDS, where participation in research represented a last chance for treatment. Physicians were eager to find research opportunities for their patients.
29. The attractiveness of student volunteers is also due, in large part, to their perceived eagerness to participate for financial reimbursement.
30. For further discussion, see Getz, K. and Kennon, A. “Surf’s Up: An Update on Recruiting Subjects via the Internet,” *Applied Clinical Trials* 1998 May; 58-61.
31. The National Institutes of Health launched a website [www.clinicaltrials.gov, accessed Apr. 2000] containing an online database of clinical trials, sponsored both by the government and private industry, in February, 2000. In addition, Centerwatch.com has recently announced its joint venture with americasdoctor.com to post trials. Drkoop.com formed an alliance with Quintiles, one of the leading CROs, to post its trials through the drkoop.com website.
32. For example, see: R. Saltus, “Sign-up Starts for Trials of Cancer Drug,” *Boston Globe*, 28 September 1999, p.A1. and L. Miller, “Cancer Victims Flood Phone Lines for Shot at New Drug,” *AP Newswire*, 28 September 1999.
33. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. (Washington, D.C.: U.S. Government Printing Office, 1978.) DHEW Publication No. (OS) 78-0012. Reprinted in *Federal Register* 44 (April 18, 1979): 23192.
34. Ibid.
35. In one report on effective strategies for recruiting subjects, the author outlined this point and stated, “panelists are eager to participate if they think they may receive a new treatment or possibly even a new cure.” Shiffer, M. “Strategies for Recruiting Research Subjects,” *Applied Clinical Trials* 1994;3(5):54-61.
36. A marketing group, in an advertisement to sponsors and investigators, offered its services for “consulting in the advertising development process to help insure that ads are persuasive and compelling— yet will pass IRB scrutiny.”
37. One coordinator we spoke with mentioned calling a number she found in a newspaper ad and finding that the receptionist mispronounced the inclusion/exclusion criteria.
38. The IRB official also told us that his IRB could have taken the position that either the ad would be changed or they would not allow the research to be conducted at their site. However, the IRB agreed that it did not want the ad to be the deciding factor over whether or not the research took place.

39. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, D.C.: U.S. Government Printing Office, 1978. DHEW Publication No. (OS) 78-0012. Reprinted in *Federal Register* 44 (April 18, 1979): 23192.
40. For a discussion of these concerns, see: Isidor, J.M., Kaltman, S.P., “Fast Track to Disaster: Considerations Raised By Current Techniques for Recruiting Clinical Research Subjects,” *Food, Drug, Cosmetic and Medical Device Law Digest* 1998; 15(1): 21-22.
41. Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: A Time for Reform* (OEI-01-97-00193), June 1998.
42. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, D.C.: U.S. Government Printing Office, 1978. DHEW Publication No. (OS) 78-0012. Reprinted in *Federal Register* 44 (April 18, 1979): 23192.
43. Advisory Committee on Human Radiation Experiments, *Final Report*, (Washington, D.C.: U.S. Government Printing Office, 1995).
44. This dual role may also be confusing for the physician-investigators; many physicians believe they are doing the best for their patients by enrolling them in research. See Miller, F. et al. “Professional Integrity in Clinical Research,” *The Journal of the American Medical Association*, 28 October 1998; 280(16):1449-1454.
45. For further discussion of these concerns, see Lind, S. “Finder’s Fees for Research Subjects,” *The New England Journal of Medicine*, 19 July 1990; 323(3):192-195.
46. There is Federal legislation that highlights concerns in this area, though not specifically directed to the clinical research process. The anti-kickback statute forbids physicians or other health care providers from receiving inducements to provide services reimbursable under the Federal health programs (i.e., Medicare and Medicaid). However, though the statute is not explicitly directed to clinical research, the statute may become more of an issue if, in the future, the Health Care Financing Administration reimburses for clinical research under Medicare as is currently under debate. [42 U.S.C. § 1320a-7b]
The Stark I and II laws (Omnibus Budget Reconciliation Act of 1989 (P.L. 101-508) and the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66), respectively), which limit self-referral to certain entities, also highlight concerns about the potential impact of financial incentives on physicians’ referring practices. The statutes are applicable only to certain types of providers (i.e., clinical laboratory or imaging services), but are based on observations that physicians with a financial stake in a providing entity more often refer their patients for these services than those that lack such ownership.
47. Box citation: Westrick, J. “Effective Subject Recruitment,” *Applied Clinical Trials* 1997; July:41-44.

48. Noble, H. “Hailed as a Surgeon General, Koop Criticized on Web Ethics,” *The New York Times*, 4 September 1999.

49. For further discussion on this topic, see: Dickert, N and Grady, C. “What’s the Price of a Research Subject? Appropriate Payments for Research Participants,” *The New England Journal of Medicine*, 15 July 1999; 341(3):198-203. and Ackerman, T. “An Ethical Framework for the Practice of Paying Research Subjects,,” *IRB* 1989; 11(4):1-4.

50. Shiffer, M. “Strategies for Recruiting Research Subjects,” *Applied Clinical Trials* 1994; 3(5):54-61.

51. Patient-identifiable medical records that are electronically maintained or transmitted would fall under the proposed regulation’s definition of “protected health information.” Therefore, the proposed rule would establish conditions for researchers’ access to such medical records to identify potential subjects. Thus, the release of this information to researchers would require either prior authorization by the respective patients or documentation of approval by an IRB or privacy board, as specified in the proposed regulation. [*Standards for Privacy of Individually Identifiable Health Information* announced in: 64 Fed. Reg. (No. 212), 3 November 1999.] The General Accounting Office also identified limitations in the IRB oversight of medical records privacy and the Common Rule in its recent report. [U.S. General Accounting Office, *Medical Record Privacy: Access Needed for Health Research, but Oversight of Privacy Protections Is Limited*, GAO-HEHS-99-55, February 1999.]

52. Concerns about confidentiality are not limited to patients. A recent highly publicized case involved researchers contacting the younger brothers of males convicted through the juvenile court system. Researchers obtained the records, and identities of the offenders, through a review of court records and the boys’ probation officers. *Institutional Review Boards—A System in Jeopardy: Hearing Before the Subcommittee on Human Resources of the House Committee on Government Reform and Oversight*, 105th Cong., June 7, 1998 (statement of B. Timothy Walsh, M.D., Co-Chair, New York Psychiatric Institute Institutional Review Board).

53. This concern is amplified by the influx of new, and inexperienced, investigators into clinical research. Without experience or training, investigators may not understand the importance of eligibility criteria and/or who meets these criteria, not to mention what constitutes a reportable adverse event. These departures from good clinical practice have potential implications for human-subject protections as well as data validity and study results.

54. Most notable among these are the cases of two Georgia researchers, known as high enrollers in the research industry, convicted of fraud in 1998 and a California physician convicted in early 1999.

55. FDA recently issued regulations requiring clinical investigators to disclose certain financial conflicts of interests to the FDA. However, draft guidance for industry states that “[recruiting incentives such as enrollment bonuses] do not meet the definition of compensation that may be affected by study outcome (which as used in the rule refers to study results) and therefore are not reportable under the rule.”

See FDA Draft Guidance for Industry [<http://www.fda.gov/oc/guidance/financialdis.html>, accessed Dec. 1999] announced in: 64 Fed. Reg. (No. 206), 26 October 1999.

56. National Institutes of Health, Office for Protection from Research Risks, *Protecting Human Research Subjects—Institutional Review Board Guidebook*, 1993.

57. Ibid. The OPRR Guidebook for IRBs includes a discussion of: concerns relating to dual patient-subject and physician-investigator roles (p.3-24), finding potential subjects through databases (pp. 3-35 and 3-36), contacting them through letter and telephone (p.4-20), and offering free health care to research participants (p. 3-45).

58. Ethics Subcommittee of the American Academy of Neurology, “Position Statement: Ethical Issues in Clinical Research in Neurology,” *Neurology* 1998 March; 50:594.

59. American College of Emergency Physicians, “Policy Statement: Code of Ethics for Emergency Physicians” (June 1997) and “Policy Statement: Gifts to Emergency Physicians from the Biomedical Industry” (reaffirmed March 1997).

60. American Academy of Family Physicians, *Compendium of AAFP Positions on Selected Health Issues*, “Fees,” “Confidentiality,” and “Proprietary Practices.” [<http://www.aafp.org/policy>, accessed Dec. 1999],

American Association of Neurological Surgeons, *Code of Ethics*, American College of Physicians, *Annals of Internal Medicine Position Paper-- Ethics Manual*, 4th edition, April 1999.

[<http://www.acponline.org/journals/annals/01apr98/ethicman.html>, accessed Dec. 1999],

American Medical Association, *Current Opinions of the Council on Ethical and Judicial Affairs*, A-99 Edition, American Psychiatric Association, *The Principles of Medical Ethics with Annotations Especially Applicable to Psychiatry (and Addendums)*, 1998 Edition, American Society of Anesthesiologists, “Guidelines for the Ethical Practice of Anesthesiology,” amended October 1997. [<http://www.asahq.org/standards/10.html>, accessed Dec. 1999].

61. FDA Office of Regulatory Affairs, “Guidance for Industry: Guideline for the Monitoring of Clinical Investigations,” Jan. 1988, p. 3. See [http://www.fda.gov/ora/compliance_ref/bimo/clinguid.html, accessed Dec. 1999].

62. 21 CFR § 312.52.

63. This phenomenon has also been cited in the literature. A legal compliance officer for a pharmaceutical company stated, “...While few people wish to acknowledge it, [monitors] and

auditors sometimes are placed in the awkward position of reporting on non-compliance by important and influential investigators, which can put a company in the uncomfortable position of having to confront the alleged offender, who may be a very important customer. Thus, there can be a tendency either to ‘rationalize’ why these issues are not signs of non-compliance or to ‘encourage the [monitors] or auditors to downplay the significance of their original findings.’ Whitelaw, S.B. “Evaluating IRBs and their Roles,” *Food, Drug, Cosmetic and Medical Device Law Digest*, 1999;16:20.

64. Food and Drug Administration, “FDA Inspections of Clinical Investigators,” *FDA Information Sheets*, September 1998.

65. Food and Drug Administration, “FDA Institutional Review Board Inspections,” *FDA Information Sheets*, September 1998.

66. This number is an estimate. Because IRBs are currently not required to register with FDA, no one, including FDA, knows the exact number of IRBs in this country.

67. According to FDA officials, FDA lacks the authority to inspect foreign IRBs. Even if FDA had the authority to inspect these foreign entities, their enforcement ability is limited.

68. Similar language is used in both FDA and overall HHS regulation (see, 21 CFR § 50.20 and 45 CFR § 46.116, respectively).

69. A recently convened forum of medical and health Internet sites met to discuss appropriate ethical guidelines for their sites around such issues as privacy, content, and sponsorship. Chin, T. “Health Sites to Develop Ethics Guidelines,” *American Medical News*, 8 November 1999; 42(42):1.

70. The Information Sheets are currently being revised. Additional recruitment guidelines may appear in them.

71. A call for increased representation of independent members corresponds with OPRR’s recommendations to one institution following an investigation in which OPRR cited the institution for inadequate review of recruiting practices.