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NIH CLINICAL TRIALS

Various Factors Affect Patient Participation



**Health, Education, and
Human Services Division**

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The Honorable James M. Jeffords
Chairman, Committee on Health, Education,
Labor, and Pensions
United States Senate

The Honorable Joseph I. Lieberman
United States Senate

Clinical trials generate the evidence base for decision-making in all areas of medicine, and they can be especially important for patients with serious or life-threatening health conditions that have limited treatment options. For those patients, participation in a clinical trial—a formal investigation of the effects of an experimental intervention on people—may offer the best chance of finding an effective treatment. Concerns have been raised that patient access to trials has become increasingly constrained as the financing of health care has changed. These concerns stem, in part, from researchers' reliance on insurance payments for the standard, nonexperimental patient care¹ provided in clinical trials as well as health plans' efforts to minimize their financial exposure. In response, the Congress is considering legislation that would require health plans to pay for the nonexperimental care provided to patients in federally approved clinical trials.

At your request, we conducted a review of patient access to clinical trials sponsored by the National Institutes of Health (NIH). Specifically, you asked us to examine (1) how health insurers' coverage policies and practices affect patient participation in clinical trials, (2) researchers' experience in enrolling patients for trials sponsored by the National Cancer Institute (NCI) and factors that may explain this experience, and (3) whether NIH has evidence of recent difficulties in enrolling patients in clinical trials.

To address these issues, we obtained information from health insurers, researchers, and NIH officials. We interviewed medical directors at 26 private health insurers that together reflect the distribution of enrollment nationally in preferred provider organizations, health maintenance

¹Standard, nonexperimental patient care includes those medical services that patients would receive for their condition regardless of whether they received the experimental treatment. Such services include physician visits and prescription drugs, for example. While there is not complete agreement on which particular services constitute standard, nonexperimental care for any particular condition, there is agreement that such care should be provided to patients. In this report we refer to this care as "standard care."

organizations (HMO), and point-of-service plans. In addition to discussing the indemnity products offered by some of these plans, we also contacted a large indemnity plan. HMOs were further distributed to reflect three size categories (plans with under 100,000 enrollees, those with 100,000 to 250,000 enrollees, and larger plans) and various model types. Also, plans were selected to provide distribution across geographic areas to include different levels of managed care activity. We also interviewed directors or their designees at 11 of the 48 NCI-designated clinical and comprehensive cancer centers that were chosen to represent different types of institutions as well as geographic diversity, concerning their trial recruitment experience. (App. I contains a list of health plans and cancer centers that participated in our review.) Although neither the insurers nor the cancer centers were statistically representative groups, and thus the findings from our interviews cannot be generalized, the findings from these two groups of interviews were consistent. In addition, we obtained information from NIH officials and officials at several NIH institutes on the recruitment and enrollment of trial participants. We also reviewed clinical trial monitoring reports. Finally, we conducted a review of the health care literature on barriers to patient participation in clinical trials and spoke with representatives of patient advocacy organizations. We performed our work from September 1998 to August 1999 in accordance with generally accepted government auditing standards.

Results in Brief

While policies generally exclude coverage for clinical trials, nearly all the insurers we interviewed allow for exceptions following case-by-case reviews by the insurers' medical personnel. If coverage is approved, insurers generally agree to pay the standard, nonexperimental care costs associated with a trial; but because there is little agreement on which trial services constitute standard care, payments can vary from insurer to insurer. Given the uncertainty about approval and payment levels, patients and physicians can be discouraged from seeking prior approval from insurers. Insurers report that they receive few requests for clinical trial coverage and that they do not maintain data to separately track such requests. Yet, insurers may pay for medical care in trials because they are unaware it is provided in a research context.

Most cancer research centers we contacted said they did not experience what they considered to be serious difficulties enrolling adequate numbers of patients for NCI-sponsored clinical trials. But all the centers described clinical trial enrollment as challenging, in part because of the significant administrative burden incurred in dealing with health insurers about trial

coverage and payment issues. Paperwork requirements can be labor-intensive and time-consuming when staff physicians and nurses must document the necessity of enrolling each patient and negotiate the specific services and amounts to be paid as standard care. Center representatives also cited an array of physician- and patient-related factors that affect the availability of patients for NIH-sponsored clinical trials. For example, community physicians may be unaware that clinical trial opportunities exist or lack the time and resources to evaluate candidates for trials. Some patients want the promise afforded by new or untested treatments but may be unable to participate because of a trial's eligibility criteria or constraints on patients' time and resources. For many other patients, uncertainty about the benefits and risks of experimental treatments can make clinical trials unattractive.

NIH has expressed concern that trial enrollment is declining, but the data provided to us by several of the largest institutes did not document the basis for NIH's concerns. Patient enrollment in the NIH-sponsored clinical trials for which we could obtain data appeared to be meeting the goals of those trials. In 1998, NIH officials reported to the Office of Management and Budget that patient participation in trials was a substantial problem, particularly for cancer trials. They cited 1996 testimony from clinical investigators that managed care seemed to have affected patient participation in cancer clinical trials. Beyond such anecdotal information, however, NIH does not have quantitative data that indicate that patient enrollment has slowed or that trials have been delayed or prematurely closed because of patient enrollment problems. Information on heart disease and diabetes trials at two other NIH institutes shows that most trials were close to meeting their recruiting targets as of the fall of 1998.

Background

A clinical trial is a method for testing new approaches to disease prevention, diagnosis, or treatment. The number of clinical trials has increased dramatically over the years.² NIH and pharmaceutical companies are the major sponsors of clinical trials that focus on assessments of new drugs, devices, and vaccines. NIH-supported trials also may address prevention strategies and surgical procedures and may target special populations, such as patients with rare diseases. Research groups at academic and other medical centers typically organize NIH clinical trials, but patients may enter into trials in a range of settings, including community hospitals and physicians' offices. The pharmaceutical industry

²For example, between 1975 and 1980, the results of six randomized controlled trials a year were published in the area of heart disease. In contrast, between 1993 and 1997, the results of 149 randomized controlled trials in the area of heart disease were published each year.

supports the majority of large clinical trials that determine therapeutic efficacy of new drug products. These trials generally focus on conditions that affect large numbers of people. An official of the Pharmaceutical Research and Manufacturers Association has estimated that drug trials represent about 75 to 80 percent of all approved trials in the United States and that pharmaceutical companies sponsor about 80 percent of all drug trials. The association also has estimated that trials of medical devices represent less than 5 percent of all approved trials and that nondrug therapies, such as new surgical or radiation treatments, represent about 10 percent.

Many clinical trials provide standard, nonexperimental treatment along with an investigational drug or procedure. In cancer care, for example, trials typically consist of modifications to standard care, such as an added drug or adjustments to the combination, dosage, and timing of drugs. In other trials, there can be significant variations from standard care, or alternative treatments, such as surgical lung volume reduction for emphysema or bone marrow and stem cell transplants for leukemia and other conditions, may be evaluated. The cost of care in a trial, relative to the cost of standard care, depends on the nature of the trial. A recent study of cancer chemotherapy trials at the Mayo Clinic found that the additional costs of clinical trial protocols may not be great: at 1 year after trial enrollment, average costs per patient were \$24,645 for trial enrollees compared with \$23,964 for comparable patients receiving standard care.³ Trials involving treatments such as bone marrow transplants, however, can be very costly.

The sponsors of a clinical trial, whether NIH or private industry, pay for research costs, such as for data collection and management, research physician and nurse time, tests performed purely for research purposes, and often the experimental therapy as well.⁴ Trial sponsors typically rely on insurers to pay for usual patient care costs, such as for doctor visits, hospital stays, laboratory tests, and X rays—costs that are incurred whether a patient is participating in a trial or receiving standard treatment. There may be uncertainty, however, about coverage of extra care costs associated with clinical trial participation, such as for additional tests.

³See Judith L. Wagner, Steven R. Alberts, Jeff A. Sloan, and others, "Incremental Costs of Enrolling Cancer Patients in Clinical Trials: A Population-Based Study," *Journal of the National Cancer Institute*, Vol. 91, No. 10 (May 19, 1999), pp. 847-53.

⁴A 1999 survey conducted by the American Society of Clinical Oncology, a professional society representing cancer physicians and researchers, showed that research costs per patient ranged from \$581 to \$5,028 for government trials and from \$569 to \$6,567 for industry trials. NCI paid an average of \$750 per patient, while pharmaceutical companies paid an average of \$2,500 per patient.

Insurers' willingness to pay for medical services associated with trials may affect patients' ability to participate. (For a discussion of clinical trial coverage policies in Medicare, the Department of Defense, and the Department of Veterans Affairs, see app. II.)

In order to increase patients' access to clinical trials, efforts are under way to strengthen links between research entities and insurers. In December 1998, NIH and the American Association of Health Plans finalized an agreement that encourages member plans, on a voluntary basis, to refer patients to trials and cover the costs of standard patient care in NIH-sponsored clinical trials. Members of the Congress and the administration have shown interest in requiring public and private payers to cover standard care costs for insured individuals enrolled in clinical trials, particularly cancer trials. Bills have been introduced in the House and Senate to this end,⁵ and a number of states also have taken action. In July 1999, the Senate approved a bill that would require self-funded health plans to cover standard patient care costs in cancer clinical trials. The Balanced Budget Act of 1997 required the Health Care Financing Administration (HCFA) to contract with the National Academy of Sciences for studies of extending Medicare benefits in five areas, including standard patient care in clinical trials. Under that contract, the National Academy's Institute of Medicine is examining the current status of clinical trial reimbursement and may recommend changes in Medicare policy in a report to be released in November 1999.

Insurers Report Coverage of Clinical Trials on a Case-by-Case Basis

As a general rule, health insurance policies exclude coverage of clinical trials. However, most insurers we interviewed indicated that they allow for exceptions to be made selectively following a case-by-case review.⁶ None of the plans we contacted provided us with data on the numbers of requests considered or cases approved, saying they do not track requests for trial coverage or their disposition separately from other benefit coverage disputes.

Once coverage is approved, insurers told us they often negotiate payment amounts for the standard, nonexperimental care given to trial participants,

⁵Bills on this issue introduced in the 106th Congress include the Medicare Clinical Trial Coverage Act of 1999 (H.R. 61) and the Improved Patient Access to Clinical Studies Act of 1999 (S. 117).

⁶Our findings are similar to those reported in a 1995 NIH study, prepared at the request of the Congress. That study was based on a survey of high-level executives (including vice presidents and medical directors) of nine major third-party payers representing indemnity insurers and managed care plans. See NIH, "Third-Party Reimbursement Policies for Clinical Trials: Survey Report" (Bethesda, Md.: Jan. 1995).

but insurers vary in how they define “standard care.” Although the uncertainty of insurer approval and payment decisions may discourage participation in clinical trials, insurers may unknowingly pay for trial-related care for patients who enroll without their insurers’ explicit approval.

While Policies Generally Exclude Coverage, Insurers Claim to Review and Approve Some Trial Services

Patient participation in NIH clinical trials often depends on prior approval by insurance plans of the proposed treatment. Typically, the request for approval initially is submitted to the insurer’s benefits manager, accompanied by information on estimated charges, the clinical assessment of the patient, data from the literature on outcomes, a description of the protocol, and the consent form. Denials are routinely appealed by the attending physician to the medical director of the insurance plan.

Denials are generally based on the grounds that health insurers consider clinical trials to be “investigational and experimental” care and, as such, are excluded from coverage.⁷ In addition, insurers sometimes deny coverage because they consider standard treatment in clinical trials to be ineligible for payment, despite the fact that most insured patients would be receiving some form of treatment if they were not in the trial. According to a leading expert on patient recruitment for clinical trials, insurers might deny all coverage for patients participating in a trial of combination drug therapy for cancer treatment if, for example, one of the four drugs in a trial was not approved by the Food and Drug Administration.

Medical directors for most of the 26 insurance plans in our interview group reported policies that exclude clinical trials from benefit coverage, but these medical directors also reported willingness in some cases to consider coverage for plan members participating in trials. Some managed care plans, in addition, have special programs that support limited patient participation in clinical trials. One large national plan, for example, has a terminal illness program that allows a plan member with a life-threatening illness to be approved to participate in a clinical trial.⁸ Another large plan has established a nationwide program that refers members needing organ and bone marrow transplants to selected clinical trials.

⁷Coverage policies, including those dealing with investigational and experimental treatments, are specified in the contracts between the insurer and the purchaser of the insurance, which is usually an employer.

⁸In December 1998, this plan also agreed to participate in an NIH-supported cancer coalition demonstration project to study the costs for members enrolled in cancer prevention and treatment trials. During the first 6 months, only one patient participated in this program; a second patient is undergoing eligibility review.

All but one of the plans we contacted reported having a mechanism for reviewing and approving participation in trials on a case-by-case basis. An insurer that covered over 6 million people in managed care and indemnity plans reported making no exceptions to its exclusionary policy. In general, insurers that do make case-by-case decisions prefer to review requests for clinical trial coverage individually because they perceive a great deal of variability in trial costs and quality. Several medical directors said they are wary of small, poorly designed clinical trials that may not have been subjected to rigorous peer review.

In considering individual patient requests, the plans we interviewed typically follow decision-making procedures established for determining coverage of experimental treatments. At most plans, the medical directors, an internal committee of physicians, or an independent panel of medical experts evaluates patient requests for trial services. Three plans told us that such coverage decisions are made by the medical provider groups that make up their networks when the financial risk has been transferred to those groups under capitation arrangements, but that patients have the option to appeal to the plan level. Insurers we spoke with reported that certain plan members have access to various types of external review. The Medicare program and some states, for example, require that managed care enrollees have access to an external appeals process if they are denied care. In the case of self-insured health plans, the employer, rather than the plan administrator, may be the final decisionmaker on requests for clinical trial coverage.

In conducting their case-by-case reviews, the medical directors reported considering a range of factors. The most common considerations were the scientific merit of the trial and the anticipated costs. Although none of the insurers had data on the cost of covering clinical trials, most perceived trials to be somewhat more costly than standard treatment. Medical directors for 19 plans said they would be inclined to approve coverage if a patient had a life-threatening disease and the experimental treatment offered some chance of clinical benefit. About one-third of the insurers would consider approving a prevention trial for a high-risk patient, one-third would likely deny such coverage, and the remainder would decide depending on the circumstances. Sixteen insurers mentioned their preference for NIH-sponsored phase III trials,⁹ and six indicated that they would not approve requests to participate in commercial drug company trials. Given concerns about the cost of trials, some insurers said trials

⁹Phase III trials involve relatively large patient populations (perhaps hundreds or thousands) and are designed to confirm benefits and risks and to compare the efficacy of new therapies with that of standard treatments.

conducted by providers in their networks receive preference.¹⁰ Twenty insurers reported that whether the trial treatment was provided in an inpatient or an outpatient setting was unimportant. Public pressure—as in the case of bone marrow transplantation for treatment of breast cancer—also has influenced coverage decisions.

Medical directors reported that, among the benefit disputes brought to them for reconsideration, coverage requests for clinical trials are not common. Cancer treatment is the most frequently requested type of clinical trial. Although plans generally do not track the number of clinical trial requests or their disposition, estimates ranged from as few as two cases per year at one plan with 180,000 members to several hundred requests per year at another with an enrollment of 10 million.

Insurers Report Variations in How They Decide Which Trial Services to Cover as Standard Care

Once insurers decide to cover services provided in clinical trials, they decide which services should be covered and at what payment amounts. Nearly all of the insurers we spoke with said that they pay standard care costs for approved trial participants. However, there is little agreement on which trial services constitute standard care, and, therefore, payment for services provided in a trial can vary widely. Moreover, insurers may not always be aware when services are provided in the context of a trial.

Insurers we interviewed stated that it is often difficult to distinguish expenses that constitute standard care—those services that otherwise would have been provided to the patient, absent the trial—from strictly research-related services. For example, physician visits and laboratory tests are components of standard care that would be covered by the insurer outside a trial. While the frequency of these services may increase in a trial to more closely monitor the patient, separately identifying claims for these additional services may be difficult. Similarly, disputes may arise if a patient has an adverse reaction to an investigational drug and requires an emergency room visit or additional treatment. While 14 insurers in our group said they would cover the cost of treating medical complications, 7 said it would depend on the situation, and 4 said they would not pay for services needed to treat research-related complications.

Several insurers said they found it too burdensome to try to separate trial costs from standard care costs in the relatively few cases at issue. Therefore, once they have approved participation in a clinical trial, they

¹⁰All 11 of the cancer centers we contacted participate in managed care networks in their areas. Only three reported that one or more of the networks in their areas currently refuse to refer patients to their centers.

generally pay all patient care costs. More commonly, however, insurers negotiate what services they will cover in clinical trials and how much they will pay for them. Many insurers we talked with said they negotiate with trial researchers regarding payments for each individual case and, therefore, payments can vary considerably. In some cases, insurers negotiate an overall fee, or case rate, while in other cases they use network fee schedules, such as discounted fee-for-service rates. Typically, patients are responsible for any deductibles and copayments required under their benefit contracts.

Trials conducted by providers outside of plans' networks complicate these payment issues. Managed care plans may negotiate or even contract for coverage of an individual patient or ask the out-of-network trial provider to accept in-network provider rates. Many insurers we contacted encourage the use of their own network of health care facilities and trial providers to hold down costs. The cost of obtaining a magnetic resonance image in a research setting, for example, may be considerably higher than the cost of performing the procedure in a facility under contract with the managed care plan.

Some of the medical directors we spoke with believe that, in many cases, patients enroll in trials without prior authorization by their plans. Moreover, these medical directors acknowledged that the plans may make payments without knowing that the care was provided in the context of a clinical trial.¹¹ The directors could not estimate the extent to which this happens but suggested that it could happen frequently. Similarly, officials of the NCI cancer centers we interviewed reported that all types of insurers, including public payers, pay some claims for patients who are treated in clinical trials at their centers. In 1997, we surveyed physicians and found that Medicare reimbursed certain trial costs despite a general policy not to cover patient care associated with clinical trials. Of 186 physicians responding, all but one received Medicare reimbursement for patients in cancer trials.¹²

¹¹This observation was previously reported in Robert Mechanic and Allen Dobson, "The Impact of Managed Care on Clinical Research: A Preliminary Investigation," *Health Affairs*, Vol. 15, No. 3 (fall 1996), pp. 72-89. Another way that plans may cover care in trials without specifically authorizing it is by including academic health centers, which are known to enroll patients in trials, in their provider networks.

¹²Cancer Clinical Trials: Medicare Reimbursement Denials (GAO/HEHS-98-15R, Oct. 14, 1997).

Researchers Meet Trial Enrollment Needs Despite Many Challenges That Can Discourage Patient Participation

A shortage of patients for NCI-sponsored clinical trials does not appear to be a significant problem at most of the cancer research centers we contacted. Nonetheless, all of the centers reported incurring a significant administrative burden when dealing with health insurers over trial coverage issues for patients on a case-by-case basis. In addition, center officials cited a number of physician- and patient-related factors that can influence clinical trial participation.

Cancer Centers Report Adequate NCI Trial Enrollment Along With Some Payment Difficulties

Most of the NCI-designated cancer centers we contacted report they are able to enroll adequate numbers of patients to conduct NCI-sponsored trials, but recruitment is not without its challenges.¹³ Cancer center representatives reported a range of experiences in obtaining health plan coverage for patients enrolled in trials and said that the process is time-consuming and labor-intensive. According to most centers, third-party payments generally cover the standard care provided to trial participants but are less consistent in covering extra care costs associated with trials.

Officials at 8 of the 11 NCI-designated cancer centers we contacted around the country reported that they were not having serious difficulties enrolling an adequate number of patients in NCI-sponsored clinical trials.¹⁴ Many centers estimated that 10 to 30 percent of their patients were participating in trials. Three centers reported experiencing what they considered to be serious difficulties enrolling patients, including a variety of marketplace and clinical factors; but generally the centers were working to overcome those difficulties. Center officials cited only two examples of trials that were closed prematurely because of enrollment problems: a costly liver infusion trial and a trial of bone marrow transplantation for a serious connective tissue disease.

Nearly all the cancer center officials we interviewed reported some degree of difficulty in dealing with insurers over clinical trial coverage, but they generally characterized these difficulties as “business as usual.” These officials said their experiences varied with the individual insurers in their areas: some rejected requests for coverage, some paid fully for standard care in trials, and others frequently denied coverage for specific services.

¹³All of the centers conducted a mix of NCI- and pharmaceutical industry-sponsored trials, with NCI-sponsored trials predominating.

¹⁴Individual cancer centers in our contact group reported total numbers of open clinical trials ranging from roughly 60 to more than 400. Numbers of patients enrolled in these trials ranged from about 350 to 450 at some centers to 1,000 to 2,000 at others.

Center physicians and staff reportedly spend considerable time and effort dealing with insurance issues for patients in trials. Research physicians are required to document that the trial is medically necessary and to provide other information to justify enrollment in a trial. Officials at two centers explained that efforts to obtain coverage were enhanced when they could provide data showing that the cost of patient care in certain cancer trials was the same as or less than that of care provided outside of trials. Other officials noted that some patients at NCI-designated centers get insurance approval for trials because they know how to appeal an initial denial. It is rare, another official said, for a persistent patient to be denied coverage, because some accommodation usually is made to pay for services. As a result of these efforts, officials reported that insurers usually agreed to cover patients in trials at their centers.

Center officials stated that insurers that approve coverage generally pay for the standard care provided to trial participants. Most of the centers in our group are able to separately identify and exclude research costs (such as trial organization, administration, and data collection) and bill insurers for standard care. Insurers typically pay the centers under the same arrangements that apply to patients at the centers who are not in trials—for example, discounted fee-for-service charges or limited case rate payments. Representatives of two centers specifically stated that the payments they received from insurers were insufficient to cover the costs of standard care involved in trials. In addition to payments from private health plans, the cancer centers reported that Medicare and Medicaid also paid claims for patients in their clinical trials.

It is not uncommon for managed care plans to require that laboratory and other testing services related to trials be performed at facilities in the plans' networks. Some cancer center researchers we interviewed contend that the inconvenience of having to visit several sites of care discourages patient participation.

Many Factors Other Than Insurance Coverage Influence Patient Participation in Trials

Our cancer center interviews and the research literature indicate that many factors, in addition to insurance coverage practices, can influence patient participation in clinical trials. For example, physicians are often unaware of relevant trials or unable to meet the time and resource demands associated with enrollment activities. In addition, many patients are not interested in enrolling in trials. Other patients face eligibility limitations or logistical barriers, or are reluctant to participate in a randomized experiment. The influence of these various factors depends on

the type of disease, type of trial, phase of trial, and other unique circumstances.

Physician Awareness and Resources

Because patients rely heavily on their physicians to inform and advise them about treatment options, physicians are often the most influential factor in a patient's decision to participate in a clinical trial. However, physicians and other health care providers can be unaware of the opportunities for participation in clinical trials. Decisions regarding enrollment in trials are made locally by physicians, hospitals, and health plans and, as a result, promotion of trials within the medical community is considered key.¹⁵ Some cancer center officials we interviewed contend that managed care patients may not be referred to specialist physicians, who are most likely to be aware of clinical trial opportunities in their area. These officials reported more intensive efforts to make patients aware of trials directly, through Internet Web sites, media advertising, and other strategies.

Officials we interviewed from 8 of the 11 cancer centers, as well as oncologists recently surveyed by the American Society of Clinical Oncology, indicated that constraints on physicians' time, available research resources, and administrative support are significant factors affecting participation. The burden on physicians often includes the need to devote additional time to identifying and enrolling suitable individuals as well as the extra paperwork involved in recording baseline data and screening candidates. In a study conducted by NCI to explore reasons for low enrollment in certain breast cancer trials, community-based oncologists cited the following issues: the time it takes to obtain consent and to attend to ongoing paperwork, to explain trial criteria to the patient, and to learn the protocol; the lack of uniform standards; and the burden and expense of performing numerous tests and following up with the patient.¹⁶

Patient Eligibility, Logistics, and Attitudes

Patients who are motivated to participate in clinical trials often perceive them as an opportunity to receive superior care and make a contribution to medical knowledge. However, these patients can be held back by the narrow eligibility criteria used to select study subjects, or discouraged by

¹⁵According to the mandate of the Food and Drug Administration Modernization Act of 1997, NIH is responsible for developing a "one-stop shopping" clinical trials database that eventually will include information on publicly and privately funded clinical trials for drugs for life-threatening diseases and conditions.

¹⁶NCI, Office of Cancer Communication, "Patient Referral to the National Cancer Institute's Autologous Bone Marrow Transplantation Clinical Trials: The Physician's Perspective" (Bethesda, Md.: Aug. 1995).

logistical considerations or their own apprehensions about medical experimentation.

According to the 1999 American Society of Clinical Oncology's survey of oncologist opinion, strict trial eligibility criteria are the "single greatest barrier" to enrolling patients in trials. Patient eligibility criteria (such as the type and stage of disease under investigation and absence of other medical conditions) are necessary to define study populations and support reliable conclusions. However, when these criteria are very restrictive, they act as barriers to patient access. In 1997, the NCI Clinical Trials Program Review Group reported that there were too many exclusion criteria in the cancer clinical trials system, with the result that potential enrollees were being disqualified for seemingly arbitrary reasons from trials for which they would otherwise qualify.¹⁷ A related concern is that researchers may be inclined to select subjects who are likely to provide the best trial outcomes. A recent study of high-dose chemotherapy for breast cancer showed that, in identifying candidates for a trial, clinicians limited referrals mostly to patients who had the best chance of survival.¹⁸

Logistical concerns can also influence patients' decisions about whether to enter trials. In some cases, participation in a trial may require traveling to a distant trial site and, possibly, staying overnight or longer. Such requirements can be time-consuming and impose financial and child care burdens on individuals who may be seriously ill. Moreover, such demands can add to stress by separating patients from family support and making it difficult to meet work obligations. As one cancer center official told us, many of life's practical concerns are magnified in a clinical trial, because trials place more requirements on and offer less flexibility to the patients.

In addition, eligible patients may choose not to enroll in clinical trials because of their personal preferences for certain types of care or their limited understanding of the clinical trials system. Sound research design requires that clinical studies minimize bias by random assignment of patients to treatment and control groups. But patients who view the experimental intervention as their best hope for treatment may be reluctant to participate if they cannot be assured they will receive what

¹⁷NCI, "Report of the National Cancer Institute Clinical Trials Program Review Group" (Bethesda, Md.: Aug. 26, 1997). This study is often referred to as the Armitage report, after the panel's chairman, James O. Armitage, M.D.

¹⁸Z.U. Rahman, D.K. Frye, A.U. Buzdar, and others, "Impact of Selection Process on Response Rate and Long-Term Survival of Potential High-Dose Chemotherapy Candidates Treated With Standard-Dose Doxorubicin-Containing Chemotherapy in Patients With Metastatic Breast Cancer," *Journal of Clinical Oncology*, Vol. 15, No. 10 (Oct. 1997), pp. 3171-7.

they believe to be superior care. Further, difficulty with the informed consent process can be a factor; even patients who want to participate in clinical trials may feel overwhelmed by the treatment decision-making process involved in informed consent. According to the NCI Clinical Trials Program Review Group report, this process has become “a disclaimer for institutions rather than information for the participant” and “may be inappropriately deterring individuals from participating in clinical trials.” Finally, a lack of trust in medical research can make patients unwilling to participate. Several of our cancer center officials said that, combined with language and cultural barriers, this lack of trust can make it especially difficult to recruit minority populations.

NIH Has Little Evidence of Problems With Patient Enrollment in Trials

Citing anecdotal reports, NIH contends that insurer resistance to covering services has contributed to a significant decline in clinical trial enrollment. Yet we received little quantitative data from NIH to indicate that fewer patients are entering NIH-sponsored trials or that more trials are being delayed or cancelled. NIH does not maintain a centralized tracking system on the number of people who enroll in clinical trials each year, overall, or by institute. Therefore, we contacted some of the institutes with the most clinical trial activity for information about patient enrollment. The institute sponsoring the most clinical trial activity, NCI, could not provide reliable data to demonstrate growing difficulties in enrolling patients in cancer trials. Officials of another large institute we contacted, the National Heart, Lung, and Blood Institute (NHLBI), reported no major new difficulties in meeting patient enrollment needs; in fact, NHLBI’s monitoring data on heart disease trials showed that most were enrolling patients at or above 80 percent of target levels. In its data system for monitoring trial enrollment, NHLBI considers meeting 80 percent of target levels good progress in recruiting. Moreover, data from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) showed diabetes trials enrolling at or above target levels in 1998.

NCI Is Concerned About Difficulties in Enrolling Patients in Cancer Trials

In a 1998 paper prepared for its fiscal year 2000 budget submission to the Office of Management and Budget, NIH stated that increased resistance by insurers to covering standard care costs for trial participants had slowed patient enrollment and led to longer studies.¹⁹ Among the NIH officials we contacted, NCI officials expressed the greatest concerns about increased difficulties enrolling patients in clinical trials. Citing testimony before the

¹⁹NIH, “Current Structure of NIH Support for Clinical Trials: Responses to Questions for the Fiscal Year 2000 OMB Budget Submission” (Bethesda, Md.: Aug. 1998).

President's Cancer Panel at four regional hearings in 1996, NCI officials indicated that insurers do not want to pay for standard care associated with clinical trials, and, as a result, "the type and number of patients that get into a trial are changed; the type of clinical trial that is conducted is changed; and the speed of the trial is changed."²⁰

Although NIH has asserted that there is a crisis in patient participation in clinical trials, NCI officials could not provide reliable patient enrollment data that would enable us to determine whether enrollment in trials was declining or whether actual enrollment lagged significantly from planned enrollment levels.²¹ NCI is currently developing a standardized electronic monitoring system to track an array of clinical trial data, including planned and actual patient enrollment. However, NCI officials told us that the new reporting system, known as the Clinical Data Update System (CDUS), did not capture information on all cancer trials. For example, it included studies by cooperative groups and some individual investigators but not those conducted at NCI-funded cancer centers. CDUS developers reported that, in converting historical data from an earlier monitoring system, they had experienced difficulties with the reporting of enrollment information. In addition, only a few data submissions had been audited since the system was implemented. Because these data were not complete or adequately verified, we could not determine whether patient enrollment had slowed or trials have been delayed.

Evidence From Other Institutes Shows Little Problem With Enrollment

The NHLBI at NIH also has a high level of clinical trial activity. NHLBI officials told us that, while recruitment challenges are always present, in general the Institute has not experienced major new difficulties in meeting patient enrollment needs. Specifically, officials noted that in the few cases in which they found enrollment lagging behind schedule, they were able to provide researchers with additional funds to help them meet recruitment targets. Factors influencing patient recruitment have not changed substantially over the past 20 years, officials told us, although NHLBI does now compete more actively for patients with trials sponsored by the pharmaceutical industry.

NHLBI monitoring data support these assertions. When NHLBI's Division of Heart and Vascular Diseases reported third-quarter 1998 monitoring data

²⁰President's Cancer Panel, "Fighting the War on Cancer in an Evolving Health Care System" (Bethesda, Md.: NCI, 1997).

²¹To examine trends in overall enrollment, we requested data on all cancer trials from 1994 to 1998. To examine delays in meeting enrollment targets, we requested planned and actual enrollment data on breast and prostate cancer trials recruiting patients during 1997 and 1998.

on 19 heart trials, of 13 trials that had been recruiting for at least a year, 6 were at or above 100 percent of their patient recruiting targets; 4 were at 80 to 99 percent of their targets; and 3 were below 80 percent of their goals.²² From the Division of Epidemiology and Clinical Applications we received mid-1998 recruitment data on six heart trials that had been recruiting for at least a year. The data showed that two trials were at or above 100 percent of their targets, three were at 80 to 99 percent of their targets, and one was slightly below 80 percent. Recruitment report notes stated that this last trial is expected to finish within budget and on time.

We also contacted NIDDK. In 1997-98, two large phase III trials were recruiting patients with diabetes, the leading area of NIDDK research. The Diabetes Prevention Program—Type II (seeking 3,000 individuals at high risk for developing non-insulin-dependent diabetes) reported that, as of December 1998, the total number of participants exceeded the target recruitment level. Specific data on 21 participating clinical centers showed that 10 clinics had recruited over 100 percent of their goals, 9 had achieved between 80 and 99 percent of targets, and 2 were at 70 to 79 percent of their goals.

NIDDK officials told us that the Diabetes Prevention Trial—Type I (enrolling individuals at high risk for developing insulin-dependent diabetes) was having difficulty with recruitment. A progress report from the trial coordinating center noted that, because only a small percentage of people are eligible to participate, the trial needs to screen an estimated 80,000 to 100,000 individuals to identify 830 participants. As of November 1998, 441 were enrolled in the study—mostly people under age 20. Officials also noted that low payments to physicians—\$10 for each screened patient—may be discouraging physician referrals to this trial.

Conclusions

We did not find evidence of widespread limitations on patient access to clinical trials. Most health insurers we interviewed said they allow for coverage of trials in some circumstances, most cancer centers we interviewed reported no shortage of patients for trials, and NIH did not document significant trial enrollment problems. Nevertheless, information on the extent to which insurers cover clinical trials is not clear-cut. On the one hand, having to seek approval through a plan's review and appeals process and negotiating payment for standard care in a trial may dissuade some patients and physicians from pursuing clinical trial opportunities. On

²²Reports on new patient enrollment in 1997 and 1998 included recruitment start and stop dates, target enrollment and actual enrollment (cumulative to date and tracked against quarterly targets on a graph), and actual minority and female enrollment compared with targets.

the other hand, because of the perceived obstacles associated with obtaining insurance coverage, some patients and physicians may submit claims without identifying the services as trial-related. Consequently, insurers may be covering more trial services than they officially approve. Moreover, in addition to insurance coverage, there are many patient- and physician-related factors that affect patient participation in clinical trials.

Agency and Other Comments

We provided a draft of this report for comment to the Institute of Medicine (IOM), the American Association of Health Plans (AAHP), and NIH. The IOM and AAHP generally concurred with the information presented and offered technical suggestions that we have incorporated as appropriate. The IOM reviewer, for example, stated that our findings are consistent with information gathered over the past year for an IOM report looking at overlapping issues (related specifically to Medicare).

NIH disagreed with our conclusion that evidence of widespread limitations on patient access to NIH-supported clinical trials is lacking, stating that our study design was flawed and our results are not generalizable. In general, NIH officials argued that we should have broadened the scope of the study to include a greater number and wider range of insurers, research institutions, and investigators, as well as physicians and patients. We recognize that NIH clinical trials involve a prescribed patient population, physicians, investigators, and academic and other medical centers, and that patients may be entered into trials in a range of settings, including community hospitals. However, we focused our work on three key participants—health insurers, cancer centers, and several of the largest trial-sponsoring institutes at NIH—because they are in a strong position to illuminate the range of factors that influence patient participation in clinical trials, and to provide evidence of recent difficulties, if any, in enrolling patients for NIH-sponsored clinical trials.

Specifically, NIH argued that our data collection efforts were insufficient on several counts: (1) the 26 managed care and indemnity insurance plans we interviewed represent a small, nonrepresentative sample; (2) in addition to interviewing officials at NIH-designated cancer centers, we should have included community physicians who participate in cooperative groups, generalist and specialist physicians who do not regularly refer patients to trials, and researchers who did not receive NIH funding; (3) we should have surveyed patients to determine factors that influence their decisions to enroll in clinical trials; (4) in addition to gathering data about insurance policies, we should have documented health plans' policies on physician

referral patterns and productivity; (5) we should have used additional data from NCI on actual and projected enrollment for clinical trials; and (6) we should have documented the need for additional resources to recruit patients into trials.

As we noted in the report, the results of our insurer and cancer center interviews should not be generalized because these groups were not statistically representative. Nonetheless, the information reported to us by health plan medical directors and cancer center directors was consistent. Insurers were selected to represent a variety of plan types, sizes, and geographic areas, and they included many large, nationwide plans. The cancer centers likewise reflected geographic diversity and different levels of managed care activity.

We did not seek out researchers and physicians who were not successful in obtaining NIH funding for proposed clinical trials. There are many reasons that researchers' proposals do not receive support from NIH, and a perceived inability to recruit a sufficient number of research subjects may play a role in the funding decision. However, our focus was on factors that affect the ability of patients to participate in trials that do receive funding from NIH institutes, and by and large, the cancer centers we contacted reported no major difficulties enrolling patients into trials.

A survey of patients with cancer or other serious diseases would have been especially problematic, given concerns about confidentiality of medical information. Instead, we discussed with cancer center directors the patient-related barriers to participation, reviewed the literature on factors that affect patient enrollment in clinical trials, and interviewed patient advocacy groups. From these sources, we learned that trial eligibility criteria can limit patient access, and practical matters such as additional demands on patients' time and resources, as well as uncertainty about the benefits and risks of experimental treatments, sometimes discourage patients from participating in trials.

A review of health plans' policies on physician referral rates and productivity was beyond the scope of our study. The results of a recently completed survey by the American Society of Clinical Oncology may shed light on these issues when published later this year. Other research is under way to develop data on several other aspects of the clinical trials issue, including the impact of managed care on academic health centers' ability to do clinical research.

We asked NCI for data that would enable us to determine whether (1) overall enrollment in cancer trials declined over the past 5 years and (2) recent breast and prostate cancer trials were meeting patient enrollment targets or were requiring more time than planned to do so. Although NCI provided partial data to us, we decided that the data were not usable for assessing patient enrollment patterns. In discussions between our statisticians and the head of the Drug Management and Authorization Section of the Cancer Therapy Evaluation Program and other NCI officials, our data experts determined that the NCI data system is in transition and the trial-specific database was incomplete, inconsistent, and had not been adequately verified. We therefore concluded that NCI did not have reliable, quantitative information documenting problems on patient enrollment.

In discussions with NCI, NHLBI, and NIDDK, none of these institutes cited an increasing use of administrative supplements as an indicator of enrollment problems. Officials at one of the smaller institutes, the National Institute on Aging, reported that it had been forced to add additional funds to clinical trial grants to support more extensive minority patient recruitment efforts than anticipated. However, they said that, in general, investigators were not experiencing major patient enrollment problems.

Appendix III contains the general comments received from NIH. In addition, the agency provided a number of specific suggestions, many of which are reflected in the final report.

As agreed with your offices, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days after the date of the report. At that time, we will send copies to interested parties and make copies available to others upon request.

Please call me at (202) 512-7119 if you or members of your staff have any questions about the information in this report. Other contributors to this study include Rosamond Katz, Ellen M. Smith, Margaret Buddeke, and Jennifer Grover.

A handwritten signature in black ink that reads "Janet Heinrich". The signature is written in a cursive style with a large initial "J" and a long, sweeping underline.

Janet Heinrich
Associate Director, Health Financing
and Public Health Issues

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Abbreviations

AAHP	American Association of Health Plans
CDUS	Clinical Data Update System
DOD	Department of Defense
FDA	Food and Drug Administration
HCFA	Health Care Financing Administration
HMO	health maintenance organization
IOM	Institute of Medicine
NCI	National Cancer Institute
NHLBI	National Heart, Lung, and Blood Institute
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
STAR	Study of Tamoxifen and Raloxifene
VA	Department of Veterans Affairs

Health Plans and Cancer Centers Interviewed

Individual Health Plans

We selected individual health plans to represent a variety of plan types—HMO, preferred provider organization, or point-of-service option—and we asked plan medical directors to focus on that selected type of plan in our interviews. However, most of the respondents reported that the same policies regarding patient participation in clinical trials generally apply to all of the plan types they offer, including indemnity plans.

Advantage Care, Inc.
Lexington, KY

Alliance Health Network
Erie, PA

Allina/Medica Health Plans
Minneapolis, MN

Blue Cross of Idaho
Boise, ID

CAPP-Care, Inc.
Newport Beach, CA

Empire Blue Cross Blue Shield
New York, NY

First Health Group, Inc.
Downers Grove, IL

George Washington University Health Plan
Washington, DC

Group Health Cooperative of Puget Sound
Seattle, WA

Group Health Northwest
Spokane, WA

Harvard Pilgrim Health Care
West Brookline, MA

**Appendix I
Health Plans and Cancer Centers
Interviewed**

Highmark Blue Cross Blue Shield
Pittsburgh, PA

M Plan
Indianapolis, IN

Pacificare of Oklahoma
Tulsa, OK

Pacificare of Washington
Seattle, WA

Penn State Geisinger
Danville, PA

PHP Companies, Inc.
Knoxville, TN

PHP of Northern Indiana
Fort Wayne, IN

Presbyterian Health Plan
Albuquerque, NM

QualChoice Health Plan, Inc.
Cleveland, OH

ViaHealth
Rochester, NY

**Corporate
Headquarters**

Aetna US Healthcare
Blue Bell, PA

CIGNA HealthCare
Bloomfield, CT

Kaiser Permanente Regional Office
Oakland, CA

Pacificare Health Systems
Santa Ana, CA

United Healthcare, Inc.
Minneapolis, MN

Cancer Centers

Barbara Ann Karmanos Cancer Institute
Wayne State University
Detroit, MI

The Cancer Institute of New Jersey
Robert Wood Johnson Medical School
New Brunswick, NJ

Cancer Research Center
Albert Einstein College of Medicine
Bronx, NY

Cancer Research Center
University of Chicago
Chicago, IL

Chao Family Comprehensive Cancer Center
University of California at Irvine
Orange, CA

Comprehensive Cancer Center
Bowman Gray School of Medicine
Wake Forest University
Winston-Salem, NC

Comprehensive Cancer Center
Yale University School of Medicine
New Haven, CT

Fred Hutchinson Cancer Research Center
Seattle, WA

H. Lee Moffitt Cancer Center and Research Institute
University of South Florida
Tampa, FL

Johns Hopkins Oncology Center
Baltimore, MD

**Appendix I
Health Plans and Cancer Centers
Interviewed**

Lombardi Cancer Research Center
Georgetown University Medical Center
Washington, DC

USC/Norris Comprehensive Cancer Center
University of Southern California
Los Angeles, CA

Clinical Trial Coverage in Federal Health Programs

Federal health programs vary in how they cover services provided in clinical trials sponsored by the National Institutes of Health (NIH). The Medicare program and the Department of Defense's (DOD) TRICARE program—both large payers—generally exclude coverage for unproven therapies, including clinical trials. The Department of Veterans Affairs (VA) and DOD's direct care system have actively promoted biomedical research for decades. VA and DOD have expanded their NIH research affiliations by developing agreements with the National Cancer Institute (NCI) to increase beneficiary access to NCI clinical trials.

Medicare

Administered by the Health Care Financing Administration (HCFA), Medicare insures 38.6 million elderly and disabled beneficiaries. Medicare's policy is that, to be covered, services must be reasonable and necessary for diagnosis and treatment of disease or injury, and they may not be experimental or investigational. Medicare does make some exceptions to its general policy not to cover patient care costs in clinical trials, particularly in the area of medical devices.²³ On the basis of a 1995 agreement between HCFA and the Food and Drug Administration (FDA), patients participating in trials of most devices that have FDA-approved Investigations Device Exemptions are eligible for Medicare payment. For example, patients receiving investigational pacemakers or defibrillators that are refinements of approved devices may be covered under the standard Medicare diagnosis-related group system that pays for both the device and the implantation procedure.

In practice, it appears that Medicare pays for a considerable amount of care provided in clinical trials. Since Medicare billing practices do not distinguish clinical trial services from standard care services, HCFA does not know how much investigational care is being reimbursed. If a patient receives chemotherapy for cancer, for example, the Medicare contractor may not know if it is provided in the context of a clinical trial. Similarly, the diagnosis-related group system for reimbursing hospital care prevents Medicare from knowing if a patient is participating in a clinical trial. HCFA would only know a clinical trial was under way if the provider purposefully notified HCFA or if an exceptional claim for reimbursement for experimental care drew attention during claims processing.

For the first time, HCFA has recently decided to provide conditional coverage of an emphysema clinical trial that examines the effectiveness of

²³Medicare also explicitly does pay for treating medical complications that may result from patient participation in clinical trials.

lung reduction surgery as a treatment. This National Heart, Lung, and Blood Institute multicenter trial has screened about 1,600 patients, and nearly 400 have enrolled so far. An NIH official, estimating that the surgery will cost approximately \$30,000 per case, told us that this demonstration project provides a good research model for third-party payers participating in clinical trials.

Under a HCFA contract, the Institute of Medicine (IOM) is conducting a study of routine patient care costs that could be incurred in clinical trials involving Medicare beneficiaries. The IOM report, which is expected to be released in November 1999, will recommend criteria that HCFA can use to determine both which services associated with clinical trials to cover as well as what Medicare payment levels should be.

DOD

The DOD health care system, administered by the TRICARE Management Activity and the Army, Navy, and Air Force, provides both direct care and contracted care for 8.2 million individuals. DOD policy excludes coverage of services considered to be unproven and restricts coverage to safe and effective treatments, but DOD does conduct medical research in its network of military treatment facilities and, since 1996, has participated in NCI clinical trials.

DOD officials relaxed the clinical trial coverage limitation in 1996 to permit access to NCI-sponsored clinical trials during a 3-year demonstration project, which was extended in June 1999. The purpose of the NCI-DOD Clinical Trials Demonstration Project is to support and expand the clinical trials conducted at the military treatment facilities and to provide beneficiaries with access to NCI clinical trials at civilian institutions.

During the first 3 years of the project, 206 patients participated in NCI-sponsored clinical trials. Over half of these patients received care for breast cancer, which, according to DOD officials, indicates that the agreement has so far been a vehicle for providing access to high technology, such as bone marrow transplantation. For instance, all patients who meet the eligibility requirements are automatically accepted into a clinical trial, and they receive the transplant without risk of being assigned to a control group. However, overall participation has been lower than expected, which has created a delay in evaluating the project: DOD officials told us that they plan to increase participation by raising awareness through education efforts. DOD officials also reported that NCI will be conducting a demonstration project evaluation that will examine

access and cost issues. Meanwhile, the new 1999 DOD agreement with NCI extends coverage to prevention clinical trials, such as the nationwide breast cancer prevention trial known as STAR (Study of Tamoxifen and Raloxifene), as well as to cancer early detection trials.

VA

A direct care provider for nearly 3 million veterans, VA actively promotes intramural and extramural medical research. Fifty-two VA medical centers maintain research affiliations with NCI, and VA collaborates on clinical research with several other NIH institutes, pharmaceutical companies, DOD, and the Department of Health and Human Services. Supported by a research budget of over \$1 billion, VA announced a major expansion of its clinical trial program in 1999.

In 1997, VA reported that cancer was the second leading cause of death among veterans. At that time, about 170,000 veterans were affected, and approximately 50,000 new cases of cancer were being reported each year. VA has responded by developing a National Cancer Strategy that expands on the already-existing relationship between VA and NCI. A key component of the strategy is an NCI-VA agreement, similar to DOD's agreement with NCI, intended not only to increase veteran access to cancer clinical trials, but also to expand opportunities for clinician participation in trials. The NCI-VA agreement allows veterans to participate in a broad range of cancer prevention, diagnosis, and treatment clinical trials.

Comments From the National Institutes of Health



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

September 13, 1999

Ms. Janet Heinrich
Associate Director
Health Financing and
Public Health Issues
U.S. General Accounting Office
Washington, D.C. 20548

Dear Ms. Heinrich:

Thank you for the opportunity to comment on the GAO Draft Report to Senator James Jeffords, Chairman of the Senate Committee of Health, Education, Labor and Pensions, and to Senator Joseph Lieberman entitled, "NIH Clinical Trials: Various Factors Can Discourage Patient Participation, but Enrollment Appears Adequate." The NIH is deeply concerned that both the study design and the data collected prevent drawing any generalizable, scientifically valid conclusions from this report. The NIH has made numerous good faith efforts to apprise the GAO about the significant flaws inherent in the design of this study (Enclosure 1). The NIH's concerns have not been addressed in the Final Report to Congress.

It is difficult to imagine an issue more critical to clinical research, to NIH, and to the health of the American people, than that of maintaining the vitality and quality of the nation's clinical trial capacity. Clinical trials are the means through which innovative advances in the prevention, diagnosis, and treatment of disease and disability are tested. Numerous questions have been raised regarding unanticipated effects of the rapid changes in our health care delivery system on the nation's research capacity, in general, and on the capacity to conduct clinical trials, in particular. Frequent anecdotal reports of significant slowing in subject accrual in NIH-supported clinical trials have been a growing concern for NIH. For example, the President's Cancer Panel documented numerous accounts of serious problems in patient recruitment in four regions of the country (Enclosure 2).

Given the difficulties inherent in gathering empirical data to confirm the depth and extent to which patient access and participation in trials is a problem, the NIH welcomed GAO's effort to systematically assess this issue. Because the study contains serious conceptual and methodologic flaws, which significantly bias the study's results, the report fails to document the extent of the problem. The report itself acknowledges that "...neither the insurers nor the cancer centers were statistically representative groups, and findings from our interviews cannot be generalized..." Our major concerns are described below, and specific, page-by-page comments are included in Enclosure 3.

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A. Small, Non-representative Sample of Health Insurers Interviewed and Apparent Lack of Data Yields Non-generalizable and Unsubstantiated Study Results

GAO has based its conclusions about the effect of health insurers' coverage policies on patient participation in clinical trials on interviews with 26 managed care and indemnity insurance plans. Considering that there are over 3,000 health plans in this country, the significance of the limited and non-representative study sample size cannot be overemphasized. Most importantly, the GAO failed to ask that the plans provide data to support their statements. Most of the 26 insurers reported "...policies that exclude clinical trials from benefit coverage...they also reported willingness in some cases to consider coverage for plan members participating in trials." Substantive data to support this and other assertions are not presented in the report. It appears that the rigorous standard for quantitative documentation requested of the NIH was not required of insurers. Following a full year's inquiry, there is no systematic information about how often insurers refuse to reimburse or cover their patients for the standard care they receive in the context of a clinical trial, nor do we have any idea how often such refusals might prevent individuals (particularly economically disadvantaged or minority patients) from participating in these trials. If nothing else, the report's reference to openly acknowledged inconsistencies in insurance payments suggests that appropriate costs may be denied and may result in additional costs to patients.

B. Focus on Funded NIH Trials Misses Critically Important Information About the Reasons for Difficulties in Patient Enrollment

Because the GAO focused on NIH clinical trials that continued to receive funding, the GAO failed to gather essential information about those trials which, because of recruitment problems, did not receive continued NIH support, i.e., did not receive continuation funding. Funded NIH trials represent a subset of clinical trials in which investigators have already demonstrated success in patient recruitment. Thus, since the GAO interviewed only those researchers who have continued to receive funding, the study design excluded a critically important study group; therefore, its conclusion is based on incomplete information, is seriously flawed, and the results cannot be generalized. It is also important to note that one of the study questions was NIH researchers' experience in enrolling patients into trials. Yet, to our knowledge, only a subset of NCI cancer center investigators were interviewed, along with some researchers supported by NHLBI and NIDDK. It is difficult to understand how conclusions about NIH trials *in toto* can be reached when a subset of investigators from only three Institutes were interviewed for the study.

C. Failure to Survey Patients Renders Flawed Conclusions About Factors That Affect Patient Enrollment in NIH Clinical Trials

Congress asked about what factors influence patient enrollment in clinical trials. Yet, the GAO chose not to interview a single patient. Instead, the GAO interviewed researchers, medical directors of health plans, cancer center directors, and NIH staff. How could GAO reach a conclusion about difficulties in patient enrollment in clinical trials without interviewing patients—both those who are enrolled in trials as well as those who have not? Factors that dissuade patients from even considering trial enrollment, such as insurance barriers they may face, were not adequately evaluated and could not be determined by interviewing health insurers or even participating researchers. The report does not address the key question of whether patients receive adequate and timely information about clinical trials. Health plans

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may be disinclined to provide this type of information to patients because it could, for example, result in an out-of-network referral. If a patient doesn't know about a clinical trial relevant to his or her disease, he or she cannot participate. As these examples illustrate, the patient perspective is totally absent from the study.

D. Failure to Adequately Assess Health Plan Policies That May Affect Physician Participation in, or Referrals to, Clinical Trials

Many concerns remain regarding barriers to physician participation in, and referral of patients to, clinical trials. With increasing emphasis on how to most efficiently and quickly move patients through the health care system, physicians may not always have the time to inform patients about available trials or to determine eligibility for participation in a trial. Despite suggestions to do so, GAO failed to collect key information about health plans' policies on monitoring physician rates of referral to trials, tracking physician productivity rates, i.e., number of patients treated per hour or providing fiscal incentives related to volume of patients seen. Absent this data, there was no way of evaluating the impact of the health plan policies on physician referral to clinical trials. To this end, the NIH suggested that the GAO interview samples of both general practitioners and specialists who do not regularly refer patients to trials to provide a complete picture on factors that may affect patient enrollment in clinical trials. GAO chose not to gather this data.

E. Numerous Inaccuracies About the Ability and Willingness of NCI to Provide Accrual Data to GAO and Failure to Contact NCI Cooperative Group Investigators

There are numerous statements throughout the report that NCI was unable to provide data requested by the GAO. NCI has repeatedly indicated to GAO, including at a May 21, 1999, meeting, that it would run any and all data reports that GAO requested in addition to the data summaries that were provided giving actual and projected accrual for trials the GAO requested. In this regard, it is important to note that GAO chose to limit its interviews to Cancer Centers and did not interview Cancer Cooperative Groups. To get a complete picture of NCI trials, the GAO should have interviewed investigators from both Cancer Centers and Cooperative Groups. By not soliciting input from community physicians who are key members of NCI Cancer Cooperative Groups, important and unique data highly relevant to the question being addressed was missed. Of note, although the NCI provided data on both Cancer Centers and Cooperative Groups to the GAO, data on cooperative groups was omitted from the report.

F. Incomplete Review of Other Factors that Affect Patient Enrollment in Clinical Trials

Barriers to patient accrual to clinical trials are multi-dimensional and cannot be evaluated on the basis of a single variable. The GAO did not examine the degree to which investigators did or did not need increased resources (e.g., staff resources, increased time duration, and administrative grant supplements) to ensure recruitment of an adequate number of patients into trials. For example, GAO was informed during the course of the study that the National Institute on Aging (NIA) stated that they provided administrative supplements to investigators when accrual of minority patients turned out to be vastly

**Appendix III
Comments From the National Institutes of
Health**

Page 4 - Ms. Janet Heinrich

more expensive and time consuming than initially anticipated. This important information that bears directly on difficulties in clinical trial recruitment was not contained in the final GAO report.

* * *

In conclusion, Congress and the nation are in need of studies that examine the factors that influence patient access to clinical trials, and the extent to which changes in referral and recruitment practices may affect the clinical research enterprise. GAO's study did not meet this critical need. It is NIH's contention that the entities selected by the GAO for study made an already difficult task significantly more problematic. From the outset, the study design was fatally flawed thus rendering the conclusions of limited utility and generalizability. While the data needed to conduct a scientifically valid study are not currently available, there were opportunities for GAO to address some of the defects in the study, but they chose not to. Although GAO's study does reveal that not all of NIH sponsored trials are wholly in crisis, it cannot be concluded that there is no problem or that pro-active measures should not be considered to avert increasing problems in the near future.

I welcome the opportunity to discuss any or all points in this letter with you.

Sincerely,



Lana R. Skirboll, Ph.D.
Director
Office of Science Policy, NIH

Enclosures

cc:

Harold Varmus, M.D.
Ruth Kirschstein, M.D.
Anthony Itteilag
Richard Klausner, M.D.
Claude Lenfant, M.D.
Philip Gorden, M.D.

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