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CLINICAL RESEARCH

NIH Has Implemented Key Provisions of the Clinical Research Enhancement Act



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Abbreviations

AAMC	Association of American Medical Colleges
AMA	American Medical Association
CREA	Clinical Research Enhancement Act
CSR	Center for Scientific Review
GCRC	general clinical research center
ICs	institutes and centers
IOM	Institute of Medicine
NCI	National Cancer Institute
NCRR	National Center for Research Resources
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
OER	Office of Extramural Research
OMB	Office of Management and Budget



United States General Accounting Office
Washington, DC 20548

September 18, 2002

The Honorable Edward M. Kennedy
Chairman
The Honorable Judd Gregg
Ranking Minority Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable W.J. "Billy" Tauzin
Chairman
The Honorable John D. Dingell
Ranking Minority Member
Committee on Energy and Commerce
House of Representatives

Clinical research is critical for the development of strategies for the prevention, diagnosis, prognosis, treatment, and cure of diseases. Clinical research has been defined as patient-oriented research,¹ epidemiologic and behavioral studies, and outcomes research and health services research.^{2,3} In contrast, basic biomedical research involves fundamental investigations that do not focus directly on patients or their diseases.⁴ The National Institutes of Health (NIH) is the principal federal agency that funds clinical

¹Patient-oriented research is research conducted with human subjects or on material of human origin, such as tissues, specimens, and cognitive phenomena. It includes research that focuses on mechanisms of human disease, therapeutic interventions, clinical trials, and the development of new technologies.

²Experts consider that clinical research also covers the area of "translational research," the process by which discoveries move between the laboratory and the patient (from bench to bedside), for example, laboratory research on the brain that can be translated to the treatment of addiction or strokes.

³This is the definition the National Institutes of Health currently applies to its clinical research. However, there are other definitions of clinical research that have been developed over time, and there is still no consensus on an exact definition of clinical research. The Clinical Research Enhancement Act of 2000 used a broad and inclusive definition of clinical research that is similar to the one described here.

⁴In classifying its basic research expenditures, NIH uses the Office of Management and Budget's (OMB) definition: "systematic study directed toward fuller knowledge or understanding of the fundamental aspects of phenomena and of observable facts without specific applications towards processes or products in mind." (OMB Circular A-21, p. 279).

research, supporting individual clinical investigators, clinical trials, general and specialized clinical research centers, and clinical research training. NIH's total budget grew dramatically from about \$12.8 billion in fiscal year 1997 to an estimated \$23.6 billion in fiscal year 2002. NIH's 27 institutes and centers (ICs) each receive separate appropriations and accomplish their missions through intramural research (government scientists conducting research at NIH's own laboratories and clinics) and, to a greater extent, through extramural research (scientists conducting research at institutions outside of NIH). Scientists compete for funding from NIH, and research proposals are evaluated for their eligibility for funding by peer review study sections of primarily nonfederal scientists.

As NIH's overall budget has grown, more attention has focused on its support of clinical research. For many years there have been concerns that clinical research proposals are viewed less favorably than basic research during the peer review process at NIH and that clinical research has not received its fair share of NIH funding. Also at issue have been the declining numbers of physician-investigators and the challenges they face, such as inadequate clinical research training and high debt from educational loans. In November 2000 the Clinical Research Enhancement Act (CREA) was enacted to address some of these concerns.⁵ The act directed NIH to consider recommendations from earlier studies for enhancing clinical research and to support and expand its resources for clinical research in general and in specific ways.⁶ The act also mandated that we evaluate NIH's implementation of its provisions. To that end, we determined whether and how NIH has (1) increased its funding of clinical research and expanded its clinical research activities, (2) improved its review of clinical research proposals, (3) supported general clinical research centers

⁵P.L. 106-505, §§ 201-207, 114 Stat. 2314, 2325-30 (2000).

⁶Specifically, CREA required NIH to support and expand the resources available for the diverse needs of the clinical research community, including resources for inpatient, outpatient, and critical care clinical research; award grants for the establishment of general clinical research centers to provide additional infrastructure for clinical research and expand their activities through telecommunications and telemedicine; make grants to support clinical research career enhancement of beginning and midcareer clinical investigators, graduate training in clinical investigation, and programs of core curricula for training clinical investigators; establish intramural and extramural clinical research fellowship programs for medical and dental students and a continuing education clinical research training program at NIH; establish mechanisms for the review of applications for these new awards and fellowships; and establish a loan repayment program for clinical investigators.

(GCRC)⁷ and expanded their activities, (4) established new clinical research career development and training programs, and (5) implemented a loan repayment program for extramural clinical investigators.

To assess NIH's progress in complying with the requirements of CREA, we reviewed NIH documents and data on clinical research expenditures, peer review of clinical research, clinical research training and career development award programs, and the clinical research loan repayment program. We also interviewed officials at several offices and institutes within NIH, including the Office of the Director, the Center for Scientific Review (CSR), the National Center for Research Resources (NCRR), and other institutes. Finally, we interviewed and consulted with key stakeholders, including the Association of American Medical Colleges (AAMC), the Institute of Medicine's (IOM) Clinical Research Roundtable, and other clinical research experts. The scope of our report was restricted to NIH's implementation of CREA, and we did not evaluate the effectiveness of NIH's actions in promoting clinical research. NIH took some actions required by CREA prior to its passage. For this reason, we looked at all relevant actions taken by NIH, not just those initiated since November 2000. We conducted our work from December 2001 through August 2002 in accordance with generally accepted government auditing standards.

Results in Brief

In general, NIH reports it has increased its financial support of clinical research and that spending on clinical research has kept pace with total NIH research spending. In fiscal year 2001, NIH reported that overall it spent approximately \$6.4 billion on clinical research, or about 32 percent of its total research dollars. Total clinical research expenditures increased by 44 percent (adjusted for inflation) from fiscal year 1997 to fiscal year 2001, while the proportion of NIH's total research dollars spent on clinical research remained constant during the same time. NIH's reports of clinical research expenditures represent the best available indications of financial trends over time, but they are not precise figures because the process of counting clinical research dollars varies widely across ICs. NIH officials told us that they are working on ways to make their counting of clinical research dollars more uniform across the ICs. In response to CREA, some

⁷GCRCs are NIH-funded entities located primarily at academic medical centers that provide research infrastructure such as inpatient and outpatient beds, laboratory services, and statistical support for publicly and privately funded clinical investigators.

institutes have developed new clinical research initiatives, including funding new clinical research centers for a variety of diseases and conditions.

NIH has taken some steps to improve its peer review of clinical research applications. CSR, the center that reviews most research grant applications submitted to NIH, recently added two new peer review study sections for the review of clinical research applications, one for clinical cardiovascular science and the other for clinical oncology. For other clinical research applications, CSR officials said it is their general goal to review them in study sections in which at least 30 percent of the applications involve clinical research and in which at least 30 percent of reviewers are themselves clinical investigators. However, they stated that this goal cannot always be achieved if the number of clinical research applications in a specific scientific area is small, because reviewing applications in a study section that provides the appropriate scientific context is given priority over quantitative targets for grouping. NIH has also established peer review mechanisms at the ICs for the review of the career development and training awards established under CREA.

NIH has increased its support of GCRCs, as required by CREA, although the program has grown more slowly than NIH's overall estimated expenditures on clinical research. Funding for the GCRCs increased by 24 percent (adjusted for inflation) from \$153,521,000 in fiscal year 1997 to \$220,824,000 in fiscal year 2001, while the number of GCRCs grew from 74 to 79. NIH officials told us that the mission of the GCRCs has remained the same, but their scope of activities has increased in response to CREA. For example, most GCRCs have hired research subject advocates to strengthen the protection of human research subjects in GCRC studies, an area of heightened concern in clinical research, and some GCRCs have begun to participate in bioinformatics networks to facilitate the sharing of data and information about clinical trials and biomedical research.

NIH has established the four clinical research career enhancement award programs mandated by CREA. Three of these programs have been implemented and support new and midcareer clinical investigators and institutional clinical research teaching programs. The fourth program, which is just beginning, is designed to support graduate training in clinical investigation. NIH has also established extramural and intramural clinical research training programs for medical and dental students and clinical research continuing education programs mandated by CREA.

NIH has initiated a new extramural loan repayment program specifically for clinical investigators as required by CREA. This program was launched on December 28, 2001, and by the February 28, 2002, deadline, NIH had received 456 applications. Twenty-one of NIH's institutes plan to fund 396 loan repayment contracts, for a total of \$20.2 million, by the end of fiscal year 2002. Currently, a clinical investigator is eligible for the loan repayment program only if engaged in NIH-supported clinical research. However, NIH officials told us they have plans to broaden eligibility for the loan repayment program in fiscal year 2003 to clinical investigators who receive funding from other sources, such as other federal agencies and nonprofit foundations.

We are recommending that NIH develop a consistent, accurate, and practical way to count intramural and extramural clinical research expenditures. Having an accurate and consistent system for tracking and reporting expenditures is key to monitoring NIH's support of clinical research in the future. In its comments on a draft of this report, NIH concurred with our recommendation.

Background

In the 1990s, a number of influential studies sponsored by NIH, IOM, and AAMC and the American Medical Association (AMA) identified some major problems in clinical research and highlighted NIH's role in addressing some of these problems.⁸ First, there was a general concern that clinical research was receiving substantially less support than basic research at NIH, yet there was little systematic data to document how much, in fact, NIH was spending on clinical research. In an analysis of NIH investigator-initiated extramural grants active in 1991, an IOM committee found that 16 percent involved human research.⁹ A few years later, a panel appointed by the NIH director known as the "Nathan Panel," developed a broad definition of clinical research (the definition NIH now uses) and,

⁸NIH Clinical Research Study Group, "An Analysis of the Review of Patient-Oriented Research Grant Applications by the Division of Research Grants" (N.p., Nov. 21, 1994); IOM, Division of Health Sciences Policy, Committee on Addressing Career Paths for Clinical Research, *Careers in Clinical Research: Obstacles and Opportunities*, eds. William N. Kelley and Mark A. Randolph (Washington, D.C.: National Academy Press, 1994); NIH Director's Panel on Clinical Research, "Report to the Advisory Committee to the NIH Director" (N.p., December 1997); and AAMC and AMA, *Report of the Graylyn Consensus Development Conference* (Washington, D.C.: AAMC, Nov. 20-22, 1998).

⁹In this analysis, the IOM committee counted as human research studies involving human subjects, studies with both human subjects and fundamental research, and human epidemiologic research.

applying this definition to all NIH competing extramural research grants in fiscal year 1996, found that 27 percent of grants and 38 percent of dollars were devoted to clinical research.¹⁰ The Nathan Panel believed that this fraction of the extramural budget devoted to clinical research was reasonable and should remain about the same, as efforts to increase the NIH budget as a whole were pursued. The studies sponsored by NIH, IOM, and AAMC/AMA recommended that NIH monitor and track its expenditures on clinical research.

A second concern was that clinical research proposals, especially those from individual investigators, did not fare as well as basic research proposals in peer review at NIH. Grant applications for clinical trials, clinical research centers, and clinical research training are typically reviewed by the sponsoring institute; however, the peer review of individual investigator grant applications usually takes place centrally, within CSR. CSR has approximately 65 study sections that review research. A study section is a panel of experts established according to scientific disciplines or research areas for the purpose of evaluating the scientific and technical merit of grant applications. In 1994 an NIH-commissioned study reported that patient-oriented research applications were less likely to receive favorable reviews in CSR than laboratory-oriented research applications when reviewed in study sections with less than 30 percent patient-oriented research applications.¹¹ However when patient-oriented research applications were grouped in study sections with greater than 50 percent patient-oriented research, they fared as well as laboratory-oriented research applications. Consequently, this report recommended that study sections reviewing patient-oriented research should have at least 50 percent of such applications and that a means should be developed and implemented to collect and track data prospectively on research applications that are predominantly patient-oriented, laboratory-oriented, mixed, or clinical epidemiology and behavioral research. Similarly, the Nathan Panel recommended that panels that review clinical research must include experienced clinical investigators and that at least 30 to 50 percent of the applications reviewed

¹⁰NIH's Office of Extramural Research (OER) conducted the Nathan Panel's analysis. OER counted the entire study as clinical research if any part of the study fit the Nathan Panel definition of clinical research.

¹¹In this study, the review success of individual investigator applications from two NIH review cycles (January and October 1994 council rounds) was evaluated. The percentage of applications in the top 20th percentile was used as an indicator of review success.

by these panels must be for clinical research. The IOM committee also recommended more oversight of study section composition, functions, and outcomes pertaining to human research.

A third problem identified in these studies was the adequacy of support for the infrastructure (that is, facilities, equipment, data systems, and research personnel) for the conduct of clinical research. Since the late 1950s, NIH has funded GCRCs across the U.S to provide clinical research infrastructure—facilities, equipment, and personnel—for NIH-funded investigators as well as non-federally funded investigators conducting patient-oriented research. Interdisciplinary and collaborative research is encouraged at these centers. The Nathan Panel, the IOM committee, and others recommended increasing financial support for GCRCs and broadening their leadership role in clinical research and research training.

A fourth concern was the decline in the number of physicians conducting clinical research. According to data collected by the AMA, the number of physicians reporting research as their primary career activity fell by 6 percent from 1980 to 1997 (from 15,377 to 14,434), while the number reporting patient care as their primary career activity almost doubled (376,512 to 620,472).¹² Observers identified a variety of challenges in pursuing a career as a clinical investigator, including the indebtedness of medical students, the length of time a clinical scientist must train, the culture of academic medicine, as well as the competition from other career options. For many years NIH has supported the training of investigators through extramural and intramural predoctoral, postdoctoral training and career development awards. However, there was concern that these awards were being directed toward basic research and were not sufficiently supporting the training and development of clinical investigators. The IOM committee, the Nathan Panel, and the AAMC/AMA reports recommended that NIH provide substantial new support for clinical research training, career development, and debt relief.

¹²See Tamara R. Zemlo and others, “The Physician-Scientist: Career Issues and Challenges at the Year 2000,” *The FASEB Journal* 14 (February 2000): 221-30.

Growth in NIH's Spending on Clinical Research Has Kept Pace with Total Spending

NIH reports that it increased its funding of clinical research and expanded its clinical research activities in response to CREA. NIH estimates that it spent about one-third of its budget, or approximately \$6.4 billion, on clinical research in fiscal year 2001. Based on these estimates, the proportion of the NIH budget spent on clinical research has remained fairly constant since fiscal year 1997. NIH's estimates of clinical research expenditures represent the best available indications of financial trends over time, but they are not precise figures because the process of counting clinical research dollars varies widely across ICs. Finally, in response to CREA, some NIH ICs have developed specific clinical research initiatives.

NIH Estimates That It Spends about One-Third of Its Budget on Clinical Research

In fiscal year 2001, NIH estimated that it spent approximately \$6.4 billion on clinical research, which represented about 32 percent of total research spending (see table 1). The institutes that spent the most on clinical research in fiscal year 2001 were the National Cancer Institute (NCI); the National Heart, Lung, and Blood Institute (NHLBI); and the National Institute of Mental Health (NIMH) (see app. I). NIH's estimated expenditures on clinical research have kept pace with the overall growth in NIH's budget. As NIH's reported clinical research expenditures increased by 44 percent (adjusted for inflation) from fiscal year 1997 to fiscal year 2001, the proportion of research dollars spent on clinical research remained constant, at 32 percent, each year.¹³

¹³Dollars have been adjusted to fiscal year 1997 using the Bureau of Labor Statistics' Medical Consumer Price Index.

Table 1: Extramural and Intramural Total and Clinical Research Expenditures in Fiscal Year 2001

Dollars in millions			
	Total expenditures	Clinical research expenditures	Clinical research expenditures as percentage of total
Extramural	\$17,061.2	\$5,904.2	35%
Intramural	1,952.3	529.0	27%
Other ^a	1,293.8		
Total	\$20,307.3	\$6,433.3	32%

Note: Numbers may not add to total because of rounding.

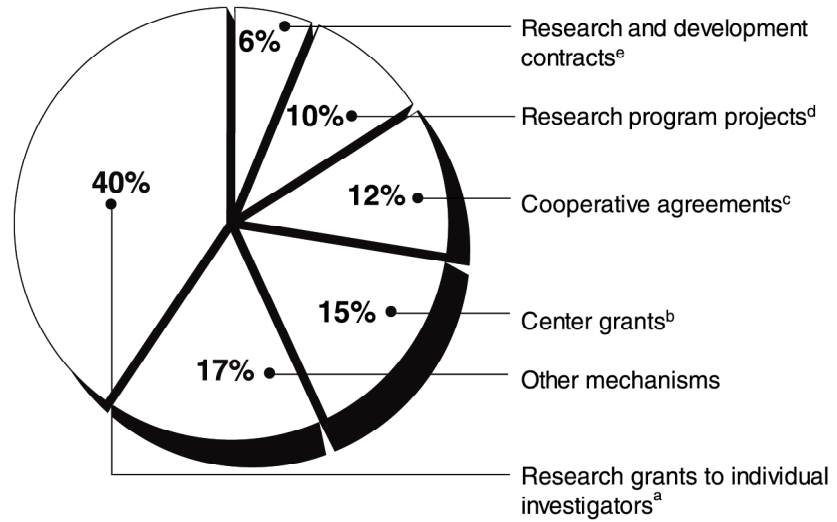
^aOther includes expenditures for Research Management and Support, Office of the Director, National Library of Medicine, and in-house cancer control activities.

Source: NIH Office of Budget.

NIH estimates that in fiscal year 2001, it spent approximately \$5.9 billion on extramural clinical research, about 35 percent of its total extramural research expenditures. NIH's extramural clinical research dollars were spent through a variety of funding mechanisms in fiscal year 2001. About 40 percent of the awarded dollars were grants to individual investigators, followed by other funding mechanisms, center grants, cooperative agreements, research program projects, and research and development contracts (see fig. 1).¹⁴ Of NIH's total extramural research expenditures for cooperative agreements and center grants, the majority of dollars were spent on clinical research in fiscal year 2001.

¹⁴NIH's estimate of \$5.9 billion spent on extramural clinical research was provided by the Office of Budget, which collects information from the ICs. However, because the Office of Budget cannot provide a breakdown of extramural research dollars by funding mechanism, the percentage breakdown of clinical research dollars by funding mechanism was provided by OER. OER's procedures overestimate clinical research expenditures because, as stated earlier, OER counts as clinical research spending all of the expenditures of a study if any part of the study fits the Nathan Panel definition of clinical research.

Figure 1: Percentage of NIH Extramural Clinical Research Expenditures by Funding Mechanism in Fiscal Year 2001



^aA discrete, defined project performed by a designated investigator.

^bSupports shared resources and facilities for categorical research by a number of investigators.

^cTypically, organized efforts of large groups of investigators and projects aimed at a specific objective.

^dOften a long-term, broad-based research program with a specific objective.

^eUsed to develop and/or apply new knowledge or to test, screen, or evaluate a product, material, device, or component.

Source: NIH Office of Extramural Research data.

In fiscal year 2001, NIH estimated that it spent about \$529 million, or 27 percent of its intramural research expenditures, on clinical research. NIH's intramural clinical research activities include research at the Clinical Center on NIH's Bethesda, Maryland, campus, as well as research by individual institutes. The Clinical Center's budget represents more than half of the intramural clinical research expenditures. The budget of the Clinical Center increased from approximately \$204 million in fiscal year 1997 to an estimated \$303 million in fiscal year 2002. This budget increase supported an increase in admissions, inpatient days, and outpatient visits.

Flaws Exist in NIH's Process of Counting Clinical Research Expenditures

NIH's reports of clinical research expenditures represent the best available indications of financial trends, but are not precise figures. The methods NIH uses to count clinical research dollars are inconsistent across ICs, potentially underestimating or overestimating its actual clinical research expenditures. Since fiscal year 1997, the Office of Budget, within the Office of the Director, has collected information from each IC on its extramural and intramural clinical research expenditures. The ICs use the NIH definition of clinical research (described earlier), but they count the dollars in very different ways. The 20 ICs that fund clinical research reported three different ways of counting clinical research dollars. First, 12 ICs count 100 percent of the grant dollars of research projects that include any clinical research. Second, one institute, NCI, codes a research project's "percent relevance" to clinical research. Projects are coded as 100 percent, major, minor, or 0 percent clinical research. If they are classified as "major," they are assigned a percentage relevancy of 50 percent, and 50 percent of the dollars are counted. If they are classified as "minor," they are assigned a percentage relevancy of 5 percent, and 5 percent of the dollars are counted. Third, 7 ICs either attempt to estimate the dollars of a research project spent on clinical research or the percentage of a project that is clinical research and apply that percentage to the total grant dollars.

These different methods of counting clinical research dollars can produce very different results. For example, given a hypothetical grant to an investigator of \$300,000 for which an IC has estimated that \$50,000 of the budget would be spent on clinical research, some ICs would report that \$300,000 was spent on clinical research; NCI could conclude that this grant has only minor relevance to clinical research and therefore would count 5 percent, or \$15,000, as clinical research dollars; the rest of the ICs would estimate that this project is about 17 percent clinical research and therefore count \$50,000 of the grant as clinical research dollars.

The Office of Budget said that the reason the ICs count clinical research dollars differently is that each developed its own methods over time, and for historical consistency, they are reluctant to change. One IC director, who heads an NIH Director's committee concerned with clinical research spending told us that NIH is working on ways to make its process of tracking and reporting clinical research dollars more consistent and accurate.

NIH Institutes Have Developed New Clinical Research Initiatives

In response to CREA, some institutes have developed new clinical research initiatives. For example, since the passage of CREA, NCI has funded two new clinical cancer centers and funded 22 new Specialized Programs of Research Excellence for different types of cancer, all of which involved early phase clinical trials. NHLBI is establishing new clinical research centers to study ways to reduce racial and economic disparities in asthma prevalence, treatment, and mortality and is funding trials to assess innovative strategies to improve the implementation of clinical practice guidelines for heart, lung, and blood diseases. The National Institute of Arthritis and Musculoskeletal Diseases has a new osteoarthritis initiative; funds multidisciplinary clinical research centers in arthritis, musculoskeletal, and skin diseases; and plans to enhance its translational research projects in children's diseases. The National Institute of Allergy and Infectious Diseases (NIAID) has continued to fund large clinical trial networks such as the AIDS Clinical Trials Group, a \$120 million per year initiative that involves research on pediatric and adult AIDS.

NIH Has Taken Steps to Improve Its Peer Review of Clinical Research

Since passage of CREA, NIH has acted to strengthen its peer review of clinical research applications. CSR established two new study sections in the areas of clinical oncology and clinical cardiovascular sciences. In study sections with a mix of clinical and basic proposals, CSR tries to group clinical research applications and reviewers, but officials could not provide data to determine how successful it has been in achieving this goal. NIH has established peer review mechanisms at the institutes for the review of career development and training awards established under CREA.

CSR Has Established Two New Clinically Focused Study Sections for Peer Review

In response to concerns that clinical research proposals are not fairly reviewed in its study sections, CSR has established two new clinically oriented study sections, Clinical Oncology and Clinical Cardiovascular Sciences. In these scientific areas, CSR found that there were a sufficient number of clinical research applications to justify separate study sections. Although the two new clinical research study sections have been welcomed by the research community, some concerns remain among clinical investigators about the fairness of the review of clinical research by other study sections that have a mix of clinical and basic research. In these study sections, CSR officials told us they try to group clinical research applications and clinical research reviewers. CSR officials told us that it is their general goal to review clinical research applications in study sections in which at least 30 percent of the applications involve clinical

research and in which at least 30 percent of the reviewers are themselves clinical investigators. CSR officials also explained that this goal cannot always be achieved because if the number of clinical research applications in a specific scientific area is small, it may not be possible to group the applications to 30 percent and still review them in a study section that provides the appropriate scientific context for review. They emphasized that reviewing applications in the appropriate scientific context is given priority over quantitative targets for grouping. CSR officials could not provide data on the extent to which they have been able to group clinical research applications and have very limited data on which reviewers are clinical investigators. The officials told us that, to date, they do not have reliable and accurate methods for identifying and tracking clinical applications or clinical reviewers.

CSR officials told us they are in the process of a broader review and restructuring of their peer review system, with input from the scientific community, to account for new developments in science.¹⁵ According to CSR, one of the goals of this reorganization is grouping applications and reviewers at 30 percent so that there is a “density of expertise” in review sections. In addition, CSR has recently appointed a special advisor on clinical research review to serve as a liaison with the clinical research communities.

Clinical Research Career Development and Training Applications Are Reviewed by ICs

To determine NIH’s response to CREA’s requirement that NIH establish appropriate mechanisms for the peer review of clinical research career development and training applications, we surveyed nine ICs that sponsored the highest number of clinical research career development awards in fiscal year 2001. We found that three ICs used a Special Emphasis Panel,¹⁶ while the six others used established committees or subcommittees to review clinical research career development and training applications. In addition, the ICs reported that most of the reviewers of these applications have clinical research experience, and

¹⁵In April 1998, CSR established the Panel on Scientific Boundaries for Review to conduct a comprehensive examination of the organization and function of the CSR review process. The panel consisted of research experts from outside NIH and incorporated extensive input from the extramural research community. Phase I of the panel, which is complete, proposed a new organizational structure for CSR, and Phase II involves the designation of study sections. Phase II is expected to be completed by 2005.

¹⁶A Special Emphasis Panel is a group of scientists chosen as reviewers because they are expert in the areas covered in the applications being reviewed.

some are involved in clinical research training. One institute brings in temporary reviewers to augment its committee if special expertise is needed. NCRR uses CSR for peer review of some career development applications that require very specific scientific expertise and therefore require review by the discipline-specific study sections of CSR.

NIH Has Increased Its Support and Scope of GCRCs

NIH has increased its support of GCRCs and GCRCs' scope of work, as required by CREA. The GCRC budget has grown over time, although more slowly than NIH's estimates of clinical research spending. Adjusted for inflation, the funding for GCRCs increased by 24 percent from fiscal year 1997 to fiscal year 2001, compared to a 44 percent estimated increase in clinical research spending at NIH during that same period. Although NIH has stopped funding some GCRCs, there has been a gradual increase in the number of GCRCs over time, from 74 in fiscal year 1997 to 79 in fiscal year 2001. There has also been an increase in the activities of GCRCs and some expansion in their scope since passage of CREA.

Funding, Number, and Activities of GCRCs Have Increased

NIH has increased funding for the GCRC program, although funding for the GCRCs has grown more slowly than NIH's estimate of overall expenditures on clinical research. From fiscal year 1997 through fiscal year 2001, funding for the GCRCs increased from \$153,521,000 to \$220,824,000 (see table 2). Adjusted for inflation, this represents an increase of 24 percent, compared to the 44 percent estimated growth in total clinical research expenditures during this period.¹⁷ The number of GCRCs gradually increased during this period, from 74 to 79.¹⁸ Funding levels for individual GCRCs in fiscal year 2001 ranged from \$712,339 to \$6.2 million, with an average funding level of about \$2.8 million. NIH officials told us that in fiscal year 2002, they are opening two new GCRCs, one at the University of Maryland and one at the University of Miami. Establishing a new GCRC costs about \$2.5 million and requires a certain threshold of investigators. Once a GCRC is set up, attracting additional investigators and research activities is easier, according to NIH officials.

¹⁷Dollars have been adjusted to fiscal year 1997 using the Bureau of Labor Statistics' Medical Consumer Price Index.

¹⁸NIH reported that in the past 15 years, it discontinued funding eight GCRCs. In some cases, GCRCs did not reapply for NIH funding. In other cases, they did reapply but did not reach a competitive funding score through the peer review process.

Table 2: Funding, Number, and Activities of GCRCs Have Increased from Fiscal Year 1997 to Fiscal Year 2001

Fiscal year	Number of GCRCs	Amount awarded (in millions)	Protocols ^a	Investigators ^b	Publications ^c	Inpatient days ^d	Outpatient visits ^e
1997	74	\$153.5	5,844	8,588	4,547	70,814	282,125
1998	75	165.4	6,072	9,083	4,385	71,309	313,100
1999	77	195.7	6,410	8,570	4,412	70,100	313,579
2000	78	198.6	6,785	9,195	5,448	65,211	328,889
2001	79	220.8	7,020	9,572	5,381	62,769	334,828

^aNumber of research studies conducted at a GCRC.

^bNumber of individuals engaged in research at a GCRC. Investigators may be supported by NIH, other federal agencies, state and local entities, or the private sector.

^cNumber of research articles published in peer review journals that used GCRC resources.

^dNumber of days human research subjects are used in research conducted at a GCRC, using GCRC facilities such as research beds and rooms.

^eNumber of visits by human research subjects who used GCRC facilities but were not hospitalized at midnight. These visits may be as short as a few minutes or as long as almost 24 hours.

Source: NIH's NCRF.

Also shown in table 2, some activities of GCRCs have increased in recent years. For example, the number of research protocols and investigators supported by GCRCs increased from fiscal year 1997 through fiscal year 2001. While the number of inpatient days funded by GCRCs declined from 70,814 in fiscal year 1997 to 62,769 in fiscal year 2001, the number of outpatient visits increased from 282,125 to 334,828 during the same period.

Scope of GCRC Activities, Including Telecommunications, Has Expanded

Since passage of CREA, NIH officials told us there has not been a change in the mission of GCRCs, but there has been an increase in the scope of GCRC activities. For example, in fiscal year 2002, 27 GCRCs have funded Clinical Research Feasibility pilot projects to support the research of beginning investigators. In addition, 76 GCRCs now each have a Research Subject Advocate who helps ensure that GCRC research is conducted safely and protects human research subjects.

CREA required that NIH expand the activities of the GCRCs through increased use of telecommunications and telemedicine initiatives. In response, NIH officials told us they increased their support of specialized bioinformatics networks that electronically link research data across GCRCs. Specifically, NCRF established a Biomedical Informatics Research Network, a computerized network that allows investigators affiliated with

GCRCs to share high-resolution images of human brains and large volumes of complex data and conduct remote analysis of the data. In fiscal year 2001, NCRR funded five bioinformatics centers at \$2.1 million, and a coordinating center at \$1.6 million, spending a total of \$3.7 million on this initiative. In fiscal year 2002, \$6 million has been set aside to extend this network. NCRR also funded a collaborative pilot project between the Cystic Fibrosis Foundation and several GCRCs, called CFnet, to assess whether clinical trials could be facilitated across GCRC sites with Web-based data handling. Based on the success of this pilot, NCRR plans to extend CFnet to 20 GCRCs and also establish a comparable network among the eight U.S. medical schools that have a high proportion of minority students to facilitate the schools' participation in clinical trials that relate to health disparities.

NIH Has Increased Its Support of Clinical Research Career Development and Training

NIH has established the four new career development award programs required by CREA. Three of these have been implemented, and the fourth is just beginning. NIH has also established intramural and extramural clinical research training programs for medical and dental students and clinical research continuing education programs as required by CREA.

NIH Has Implemented Three Award Programs for Career Development of Clinical Investigators

NIH recently established three new clinical research career development award programs for individuals and institutions outside government that are designed to increase the supply and expertise of clinical investigators (see table 3). NIH used its K award mechanism, its usual method for providing support for career development of investigators, to establish these programs. In fiscal year 1999, NIH implemented the Mentored Patient-Oriented Research Career Development Award (K23) to support investigators who are committed to conducting patient-oriented research for 3 to 5 years. In the same year, NIH implemented the Mid-Career Investigator Award in Patient-Oriented Research (K24) to provide support for more senior clinicians to relieve them of patient-care duties and administrative responsibilities so that they can conduct patient-oriented research and serve as mentors for beginning clinical investigators. The Clinical Research Curriculum Award (K30), also implemented in fiscal year 1999, supports the development and expansion of clinical research

teaching programs at institutions.¹⁹ About half of the K30 programs offer graduate degrees in clinical research (for example, masters or doctorate).

Table 3: Clinical Research Career Development Award Programs Established by NIH since Fiscal Year 1999

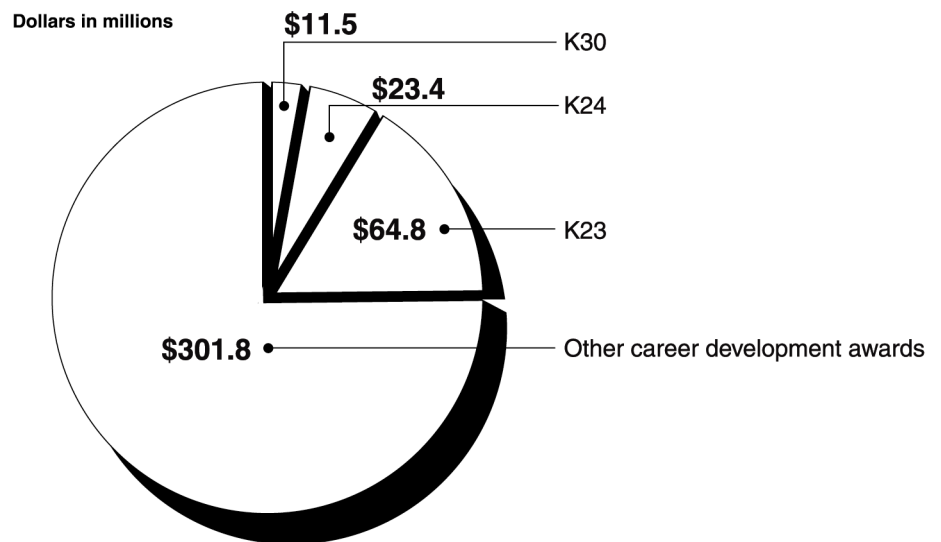
Career development award program (K award mechanism)	Purpose	Year implemented	Initial projected annual number of awards	Cumulative number of awards	Funding level (FY 2001)
Mentored Patient-Oriented Research Career Development Award (K23)	This 3-5 year nonrenewable award supports the career development of investigators who are focused on performing patient-oriented research under the supervision of a mentor. Most awards provide candidates with a salary of up to \$75,000. In terms of research support, candidates receive \$25,000 to \$50,000 per year and must give 75% minimum effort toward research career development and clinical research.	FY 1999	80	496	\$64.8 million
Mid-Career Investigator Award in Patient-Oriented Research (K24)	This 3-5 year renewable award supports clinicians in affording them the ability to devote time to clinical research and to act as mentors for beginning clinical investigators. Mentors receive up to 50% of the NIH salary cap in addition to fringe benefits. They also receive \$25,000 per year for research support and must give from a minimum of 25% to a maximum of 50% effort toward mentoring and clinical research.	FY 1999	60-80	215	\$23.4 million
Clinical Research Curriculum Award (K30)	This 5-year renewable award supports the administrative infrastructure for graduate training and expansion of clinical research teaching programs at institutions.	FY 1999	20	57	\$11.5 million
Mentored Clinical Research Scholar Program Award (K12)	This 5-year award supports an institutional career development program for physicians and dentists to acquire the skills to become independent patient-oriented clinical investigators. Candidates are provided a maximum of \$90,000 for salary support for each year commensurate with the applicant institution's salary structure for persons of equivalent qualifications, experience, and rank. This award is a one-time offering, but may be expanded.	FY 2002	Program begins in FY 2002 with 10 projected awards	Not applicable	\$6.2 million (FY 2002 estimate)

Sources: NIH Office of Extramural Programs; NIH Office of Reports and Analysis; and Request for Applications and Program Announcement Documents.

¹⁹This award program supports the administrative infrastructure for graduate training, but generally does not provide tuition/stipends to students.

The response to these new award programs was substantial, and NIH funded more awards than originally planned. NCCR and the largest institutes (for example, NCI, NHLBI, and NIMH) sponsored the highest number of the new K23 and K24 awards. NHLBI is administering the majority of the K30 awards. Although NIH has received applications for K23 and K24 awards from a variety of clinical investigators, most applicants and awardees are physicians. The K30 awards have primarily gone to academic medical centers. The new awards combined represent 25 percent of expenditures NIH allotted for all K awards under its Career Development Program in fiscal year 2001 (see fig. 2).

Figure 2: NIH's New Clinical Research Career Development Awards Relative to All NIH Career Development Awards in Fiscal Year 2001



Source: NIH Office of Reports and Analysis data.

NIH officials told us that they are initiating plans to evaluate the new clinical research career development awards and track career outcomes. The design of this assessment will be based on previous studies of training award recipients, specifically NIH's study of the outcomes of the National

Research Service Awards (NRSA)²⁰ and will rely on NIH's new electronic grant application.

Size and Scope of New Award Program for Graduate Training in Clinical Research Is Limited

In 2001 NIH announced a fourth new clinical research career development award, the Mentored Clinical Research Scholar Program (K12). This award program, sponsored by NCRR and linked to the GCRCs, is NIH's response to CREA's directive to support graduate training in clinical research. NCRR decided to start the K12 program as a small pilot project and then expand it later if successful.²¹ In fiscal year 2002, NCRR received 43 applications for this award and expects to fund 10 of these. In the first year of the program, each funded award may enroll three clinical research scholars, for a total of 30 scholars. NIH projects that the number of scholars could grow to 120 in 5 years.

We interviewed several K30 program directors who indicated that obtaining graduate tuition and stipend support for their students and prospective students was a major constraint. The K30 award, which has been well received in the research community, funds curriculum, staff, as well as tuition and other costs in special circumstances, but generally does not directly support students. Instead, students must seek funding from other NIH, federal, or private sources. An NIH official estimated that the number of formal trainees in individual K30 programs ranges from several to three dozen. This official was not able to provide data on whether these students had tuition support and what kind of support. However, the K30 program directors we talked to said some of their students had tuition support from other NIH funding mechanisms; others had support from their university. Although the new K12 program is consistent with the requirements of CREA, some K30 program directors and other experts believe the size and scope of the program will be too small to meet the need for graduate training support for clinical investigators.

²⁰NIH's Office of Research Training and Committee on Research Training Assessment obtained data on students in the biomedical and behavioral science fields who received NRSA support from 1981 through 1992. See Georgine M. Pion, *The Early Career Progress of NRSA Predoctoral Trainees and Fellows*, NIH Pub. No. 00-4900 (Bethesda, Md.: NIH, March 2001).

²¹The K12 pilot at NCRR is not the only type of K12 program being used to support clinical research at NIH. For example, NCI created a Clinical Oncology Career Development Program 10 years ago that is one of the major ways it trains investigators to do translational research as well as design and implement clinical trials.

Other NIH Clinical Research Training Programs Targeted toward Medical and Dental Students

In terms of fellowships for clinical research training, in fiscal year 2001, NCRR announced a new mentored medical student clinical research program that will support a small number of medical and dental students at GCRCs. This program provides supplemental grants to GCRCs to offer 1 year of support for medical and dental students, usually from their third through fourth year of school, in the form of salary, supplies, and tuition assistance. A total of five students may eventually be supported at each GCRC site annually, although NCRR plans to provide support for only one medical student per GCRC in fiscal year 2002.

Since 1997, NIH has also trained medical and dental students at its campus in the area of clinical research. In this program, partially supported by a pharmaceutical company, 15 to 20 students are selected each year and are each paired with a mentor for a year of academic study and clinical research experience.²²

NIH Has Established an Extramural Loan Repayment Program for Clinical Investigators

NIH has launched an extramural loan repayment program for clinical investigators as required by CREA, and most of NIH's ICs participate in the program. In the first year of implementation, eligibility for the loan repayment program was tied to receipt of NIH funding. However, in fiscal year 2003, NIH plans to extend eligibility to allow clinical investigators who receive funding from other sources, such as other federal agencies and nonprofit foundations, to apply.

²²NIH also provides ongoing clinical research training for scientists working at its Bethesda campus and other institutions. Courses include Introduction to the Principles and Practice of Clinical Research, Principles of Clinical Pharmacology, Ethical and Regulatory Aspects of Human Subjects Research, and Clinical Research Training. NIH also collaborates with Duke University and the University of Pittsburgh to offer distance-learning programs that provide clinical research training to physicians, dentists, Ph.D.'s, and allied health professionals.

New Extramural Loan Repayment Program Established by NIH

In response to CREA, NIH established an extramural Clinical Research Loan Repayment Program. This new loan repayment program joins four other extramural loan repayment programs²³ and four intramural loan repayment programs²⁴ that are administered by NIH's Office of Loan Repayment and Scholarship. The new extramural Clinical Research Loan Repayment Program was implemented on December 28, 2001, and a total of 456 applications were received by February 28, 2002. NIH plans to fund 396 loan repayment contracts for a total of \$20.2 million by the end of fiscal year 2002.²⁵ The program provides for the repayment of up to \$35,000 per year of the principal and interest of an individual's educational loans for each year of obligated service.²⁶ These individuals are obligated to engage in clinical research for at least 2 years. The clinical research loan repayment program represents a sizeable proportion (almost two-thirds) of the total extramural loan repayment program budget.

To be eligible for the clinical research loan repayment program, a clinical investigator must have received an NIH research service award, training grant, career development award, or other NIH grant as a first-time principal investigator or a first-time director of a subproject on a grant or cooperative agreement. In fiscal year 2003, the Director of the Office of Loan Repayment and Scholarship told us that NIH plans to remove the NIH-funding restriction and allow clinical investigators who receive funding from other sources, such as other federal agencies and nonprofit

²³NIH supports four other extramural loan repayment programs: Loan Repayment Program for Pediatric Research, Loan Repayment Program for Minority Health Disparities Research, Loan Repayment Program for Clinical Researchers from Disadvantaged Backgrounds, and Loan Repayment Program for Contraception and Infertility Research.

²⁴NIH's intramural loan repayment programs include a Clinical Research Loan Repayment Program as well as an AIDS Research Loan Repayment Program, a General Research Loan Repayment Program, and a General Research Loan Repayment Program for Accreditation Council for Graduate Medical Education Fellows.

²⁵During the implementation phase of the loan repayment program, NIH's ICs were instructed to assume an average cost of \$100,000 for each loan repayment contract to guide determination of how many awards they could make. However, the level of debt among potential awardees has been found to be less than what was originally thought, so NIH intends to fund more repayment contracts in fiscal year 2002 than it originally planned.

²⁶The exact amount of each loan repayment contract will vary and will depend on the total eligible debt of each awardee. Eligible individuals must have qualifying educational debt in excess of 20 percent of their annual income or compensation at their expected date of program eligibility. NIH will apply a portion of the budgeted \$20.2 million toward federal and state taxes.

foundations, to apply for the loan repayment program.²⁷ In addition, NIH expects to almost double the size of the extramural Clinical Research Loan Repayment Program in fiscal year 2003.

Twenty-one of NIH's ICs Participate in the Loan Repayment Program

Although NIH has a central office that administers all the loan repayment programs, funding for the clinical research loan repayment program was distributed to the ICs, based on reported clinical research expenditures in fiscal year 1999. Thus 21 of NIH's 27 ICs plan to participate in the program by reviewing applications and awarding loan repayment contracts (see app. II). The ICs sponsoring the highest number of contracts are NCI, NHLBI, and NIMH. NCCR also plans to sponsor a significant number of loan repayment contracts. As with most of the training and career development awards, an NIH official told us that the ICs were in the best position to assess applications and the clinical research career potential of awardees.

Conclusion

In general, NIH has complied with the key provisions in CREA. It has increased its financial support of clinical research, expanded its clinical research activities, made improvements in its review of clinical research proposals, expanded its support of GCRCs, established new clinical research career development and training programs, and begun to implement a new extramural clinical research loan repayment program. Some of NIH's actions were taken prior to CREA's passage and some are still being implemented. However, we identified some inconsistencies with the way that NIH counts clinical research expenditures. These inconsistencies limit the precision of NIH's reports of clinical research expenditures and its ability to monitor the support of clinical research.

Recommendation for Executive Action

To strengthen the tracking and reporting of intramural and extramural expenditures for clinical research, we recommend that the Director of NIH develop and implement a consistent, accurate, and practical way for all ICs to count intramural and extramural clinical research expenditures.

²⁷Federal employees will not be eligible.

Agency Comments

NIH reviewed a draft of this report and provided comments, which are included as appendix III. NIH concurred with our recommendation and reported that it is taking steps to implement a better, more unified system for tracking and reporting clinical research expenditures across the ICs. According to NIH, this new system will be implemented in fiscal year 2003. NIH also provided technical comments, which we incorporated as appropriate. In particular, NIH clarified its response to our questions about the peer review of clinical research. NIH emphasized that it recognizes the importance of collecting data on the grouping of clinical research applications and reviewers. Toward that end, NIH stated that one of the responsibilities of CSR's newly appointed Special Advisor on Clinical Research Review will be to investigate new methods to reliably identify and track clinical research applications and clinical research reviewers.

We will send copies to the Secretary of Health and Human Services, the Director of NIH, appropriate congressional committees, and others who are interested. We will also make copies available to others on request. In addition, the report will be available at no charge on GAO's Web site at <http://www.gao.gov>.

If you or your staffs have any questions, please contact me at (202) 512-7119 or Martin T. Gahart at (202) 512-3596. Key contributors to this assignment were Anne Dievler, Cedric Burton, and Elizabeth Morrison.



Janet Heinrich
Director, Health Care—Public Health Issues

Appendix I: NIH's Estimated Expenditures for Extramural and Intramural Clinical Research, by IC, Fiscal Years 1997 - 2001

Dollars in millions

Institutes and centers	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001
National Cancer Institute	\$740.0	\$750.0	\$818.4	\$941.2	\$1,045.3
National Heart, Lung, and Blood Institute	524.0	550.0	621.1	785.3	848.5
National Institute of Mental Health	474.0	498.1	493.6	549.4	729.7
National Institute of Allergy and Infectious Diseases	444.4	452.9	553.3	639.6	693.4
National Institute of Child Health and Human Development	340.4	364.5	414.8	495.5	553.8
National Institute on Drug Abuse	274.1	295.0	340.5	390.9	446.7
National Institute of Diabetes and Digestive and Kidney Diseases	222.0	238.9	272.3	312.0	357.0
National Institute on Aging	201.2	182.1	247.8	287.8	337.2
National Institute of Neurological Disorders and Stroke	232.5	218.5	259.2	286.0	259.6
National Center for Research Resources	162.0	175.2	210.0	217.6	251.1
National Eye Institute	58.7	147.0	165.9	196.0	213.5
National Institute on Alcohol Abuse and Alcoholism	0	117.5	142.7	158.7	171.2
National Institute on Deafness and Other Communication Disorders	84.7	91.0	103.1	114.4	107.9
National Institute of Arthritis and Musculoskeletal and Skin Diseases	77.7	70.6	72.5	94.8	97.9
National Institute of Nursing Research	46.4	46.4	57.7	76.5	90.5
National Institute of Dental and Craniofacial Research	63.1	62.0	66.7	74.6	78.6
National Center for Complementary and Alternative Medicine	0	0	0	32.6	60.8
National Institute of Environmental Health Sciences	35.8	39.4	44.5	50.0	55.3
National Center on Minority Health and Health Disparities	0	0	0	0	20.9
National Human Genome Research Institute	17.5	22.3	22.5	14.5	14.3
Office of the Director	0	0	13.9	0	0
Total	\$3,999.0	\$4,321.4	\$4,920.5	\$5,717.3	\$6,433.3

Source: NIH Office of Budget.

Appendix II: NIH's Extramural Clinical Research Loan Repayment Contracts by IC, Fiscal Year 2002

Institutes and centers	Number of contracts
National Cancer Institute	55
National Heart, Lung, and Blood Institute	49
National Institute of Mental Health	43
National Institute of Allergy and Infectious Diseases	30
National Institute on Aging	29
National Institute on Drug Abuse	29
National Center for Research Resources	22
National Institute of Diabetes and Digestive and Kidney Diseases	22
National Institute of Child Health and Human Development	21
National Institute on Alcohol Abuse and Alcoholism	17
National Institute of Neurological Disorders and Stroke	17
National Institute of Arthritis and Musculoskeletal and Skin Diseases	16
National Eye Institute	14
National Institute on Deafness and Other Communication Disorders	9
National Institute of Dental and Craniofacial Research	7
National Human Genome Research Institute	4
National Institute of Environmental Health Sciences	3
National Institute of General Medical Sciences	3
National Institute of Nursing Research	3
National Center for Complementary and Alternative Medicine	2
John E. Fogarty International Center	1
Total	396

Source: NIH Office of Loan Repayment and Scholarship.

Appendix III: Comments from the National Institutes of Health



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
www.nih.gov

AUG 30 2002

Janet Heinrich, Ph.D.
Director, Health Care-Public Health Issues
U.S. General Accounting Office
441 G Street, N.W.
Washington, D.C. 20548

Dear Dr. Heinrich:

I enclose the comments of the National Institutes of Health (NIH) on the General Accounting Office (GAO) draft report entitled, "Clinical Research: NIH Has Implemented Key Provisions of the Clinical Research Enhancement Act," GAO-02-965. This report provides a comprehensive evaluation of our compliance with the provisions of the Clinical Research Enhancement Act, and we are pleased that it acknowledges the substantial efforts we have made.

We concur with the recommendation to develop and implement a better system of counting intramural and extramural clinical research expenditures. Our comments identify the ongoing or planned actions we are undertaking to implement this recommendation. We also offer a series of technical comments that we believe will improve the report's accuracy and clarity.

Thank you for giving us the opportunity to review and comment on this draft report.

Sincerely,

A handwritten signature in black ink, appearing to read "Elias A. Zerhouni".

Elias A. Zerhouni, M.D.
Director

Enclosure

**Comments of the National Institutes of Health (NIH)
On the U. S. General Accounting Office (GAO) Draft Report
“Clinical Research: NIH Has Implemented Key Provisions of the Clinical Research
Enhancement Act,” GAO-02-965**

We appreciate the opportunity to review and provide comments on this draft report. The report provides a comprehensive evaluation of NIH’s compliance with the provisions of the Clinical Research Enhancement Act (CREA) and we are pleased that it acknowledges the substantial efforts we have made.

GAO Recommendation:

To strengthen the tracking and reporting of intramural and extramural expenditures for clinical research, we recommend that the Director of NIH develop and implement a consistent, accurate, and practical way for all Institutes and Centers (IC) to count intramural and extramural clinical research expenditures.

NIH Comments:

We concur. As noted in the report, the process of counting clinical research dollars varies widely across ICs. As a result, consolidated NIH reports of clinical research expenditures are not precise figures. We were aware of these issues and are working on ways to make the process of tracking and reporting clinical research expenditures more consistent and accurate. To begin, the NIH Director appointed a Committee to identify the most consistent and accurate methods to report the NIH clinical research spending. This Committee conducted an analysis that identified the variabilities among ICs in reporting funding for both intramural and extramural clinical research.

The Committee determined how it could best harmonize the different reporting systems from the various ICs. Four different methods of coding clinical portions of grants were used to assess a large and representative sample of extramural grants. Three of these four methods produced nearly identical results. As a consequence, the Committee decided that all Institutes would report their clinical research for each grant and contract and their activity on a proportional (0, 25 percent, 50 percent, 75 percent, or 100 percent) basis. These numbers for extramural clinical research will be reported by each IC through its own budget office to the central NIH Office of Budget.

With regard to intramural clinical research, each IC will report its proportional allocations (excluding Clinical Center costs) through its budget office. The total Clinical Center operational costs will be added to these numbers to determine the total intramural clinical research allocation. The intramural and extramural clinical research dollar totals will then be available through the central NIH Office of Budget. The Committee also discussed the feasibility of attributing any other core clinical costs to the NIH clinical

**Appendix III: Comments from the National
Institutes of Health**

research allocation. The Committee decided that almost all of these costs are already accounted for and considerable effort would be required to capture the very small amount of additional dollars spent. Finally, this new clinical research tracking and reporting system will be implemented in FY 2003. We believe that this will provide for a consistent, accurate, and transparent way for the NIH to report its expenditures for clinical research.

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