HARNESSING SCIENCE: ADVANCING CARE BY ACCELERATING THE RATE OF CANCER CLINICAL TRIAL PARTICIPATION

HEARING

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

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HARNESSING SCIENCE: ADVANCING CARE BY ACCELERATING THE RATE OF CANCER CLINICAL TRIAL PARTICIPATION

THURSDAY, MAY 13, 2004

HOUSE OF REPRESENTATIVES,
COMMITTEE ON GOVERNMENT REFORM,
Washington, DC.

The committee met, pursuant to notice, at 10:03 a.m., in room 2154, Rayburn House Office Building, Hon. Tom Davis of Virginia (chairman of the committee) presiding.

Present: Representatives Tom Davis of Virginia, Duncan, Murphy, Carter, Waxman, Cummings, Kucinich, Watson, Van Hollen, and Norton.

Also present: Representative Garrett.

Staff present: David Marin, deputy staff director/director of communications; Drew Crockett, deputy director of communications; Teresa Austin, chief clerk; Brien Beattie, deputy clerk; Susie Schulte, professional staff member; Corinne Zaccagnini, chief information officer; Robert White, press secretary; Kristin Amerling, minority deputy chief counsel; Josh Sharfstein, minority professional staff member; Earley Green, minority chief clerk; Jean Gosa, minority assistant clerk; and Naomi Seiler, minority staff assistant.

Chairman TOM DAVIS. Good morning. A quorum being present, the committee will come to order.

I want to welcome everybody to today's oversight hearing on cancer clinical trials. This hearing will examine the status of efforts to bring innovative cancer treatments to patients and discuss how to change the face of cancer into a less terminal and more treatable disease.

The two panels of witnesses today will present testimony on the various factors contributing to low accrual of adult patients in cancer clinical trials and what efforts are being taken to obtain reasonable participation levels to better provide more treatment options for cancer patients.

Cancer is the second leading cause of death in the United States, taking the lives of over a half million Americans each year, more than 1,500 people each day. Roughly 1.3 million new cancer cases are diagnosed in this country each year. These statistics are sobering. All of us here today know a relative or friend who has been diagnosed with some type of cancer. Anyone who has been affected by cancer understands the needs for more and better treatment options for patients.

In order for new drugs and therapies to be approved by the Food and Drug Administration, several cancer clinical trials must be conducted. Clinical trials are essential for determining safe and effective therapies in modern medicine. Early detection of cancer and the application of new treatments available through clinical research are responsible for significant improvements in cancer survival rates. Clinical trials are designed to answer scientific questions which translate into better and less toxic therapies for patients. Trials allow doctors and researchers to gain information about the benefits, side effects, possible applications, and doses of new and existing drugs.

In order for scientists and oncologists to make accurate conclusions about an experimental new drug's effect, clinical trials require the participation of numerous cancer patients. Further, research has shown that trial participants nearly always receive equivalent or better care than those receiving standard treatments, despite the experimental nature of these investigational treatments.

Clinical trials can offer patients advanced treatments that would be otherwise unattainable. Thousands of people are helped each year by joining cancer clinical trials, and millions of people have ultimately benefited from others' participation in trials.

So we pose the question to our panel of witnesses today: why do only 3 percent of adults nationwide enroll in centers when up to 20 percent are eligible? And what efforts are being taken to resolve the barriers to better clinical trials and adequate adult enrollment?

We want to examine the different scientific, logistical, and financial realities that interact and impede reasonable participation in adult trials. The lack of patient and physician education about clinical trials, problems traveling to the trial sites, strict eligibility criteria, and third party payer reimbursement policies prevent a large number of patients from participating. As a result of these contributing factors, a vast majority of cancer patients fail to even consider clinical trials when reviewing their treatment options.

We will hear today from the cancer community the urgency to reverse this situation and resolve the barriers to adequate adult enrollment in clinical trials. Clinical trials are essential for improving outcomes in cancer patients. By improving participation levels and creating more trials to new test therapies, we can transform cancer into a more treatable and less fatal disease.

The equation is simple: clinical research leads to discovery of new and better therapies for cancer patients, helping them live longer and improving their quality of life.

I know all of our witnesses this morning will agree that we need to boost participation in clinical trials. Along with improving accrual rates, we may need to consider improving other ways our health community approaches cancer. Clinical trials are just a single component of the cancer spectrum. I understand the complexity of the disease and the intricacies surrounding the discovery, development, and delivery of treatments. I look forward to a constructive dialog on this topic.

The committee welcomes our witnesses for this important testimony today.

I would now yield to my colleague, Henry Waxman, for an opening statement.

[The prepared statement of Chairman Tom Davis follows:]

Statement of Chairman Tom Davis
Committee on Government Reform
Hearing on "Harnessing Science: Advancing Care by Accelerating the Rate of Cancer Clinical Trial Participation"
May 13, 2004

Good morning. I would like to welcome everyone to today's oversight hearing on cancer clinical trials. This hearing will examine the status of efforts to bring innovative cancer treatments to patients and discuss how to change the face of cancer into a less terminal and more treatable disease. The two panels of witnesses today will present testimony on the various factors contributing to low accrual of adult patients in cancer clinical trials and what efforts are being taken to obtain reasonable participation levels to better provide more treatment options to cancer patients.

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In order for scientists and oncologists to make accurate conclusions about an experimental new drug's effects, clinical trials require the participation of numerous cancer patients. Further, research has shown that trial participants nearly always receive equivalent or better care than those receiving standard treatments, despite the experimental nature of these investigational treatments. Clinical trials can offer patients advanced treatment that would otherwise be unattainable. Thousands of people are helped each year by joining cancer clinical trials, and millions of people have ultimately benefited from others' participation in trials. So we pose the question to our panels of witnesses today: why do only 3% of adults nationwide enroll in clinical trials when up to 20% are eligible? And what efforts are being taken to resolve the barriers to better clinical trials and adequate adult enrollment?

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criteria, and third-party payer reimbursement policies prevent a large number of patients from participating. As a result of these contributing factors, a vast majority of cancer patients fail to even consider clinical trials when reviewing their treatment options. We will hear today from the cancer community the urgency to reverse this situation and resolve the barriers to adequate adult enrollment in clinical trials.

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Mr. WAXMAN. Thank you, Mr. Chairman. I am pleased to participate in this hearing on how to accelerate progress against cancer. This is a topic that I've worked on for many years. When I was the chair of the Health Subcommittee of the Energy and Commerce Committee, I was responsible for legislation reauthorizing the National Cancer Institute. We worked with experts inside and outside of the Government to improve rehabilitation services, expand research on reproductive cancers, and strengthen education and grantmaking decisions.

It has also been my priority to make sure that all Americans have access to benefits of medical progress against cancer, and I'm particularly proud of legislation that expanded access to screening for breast and cervical cancer and of legislation that provided Medicaid coverage for those who are found on screening to have these tumors.

Today's hearing highlights how much more needs to be done. Over the last several decades, while rates of heart disease have dropped dramatically, rates of cancer have largely remained stable. Despite progress against a few specific tumors, cancer will kill an estimated 500,000 Americans in 2004.

The simplest and quickest way to make a dramatic reduction in cancer in the United States is to prevent it. Every Member of Congress knows that the No. 1 preventable cause of cancer in the United States is the cigarette. Last year a committee advising the Department of Health and Human Services recommended a simple evidence-based plan to help 5 million people quit smoking and save 3 million lives. The plan was endorsed by former Surgeons General Dr. Julius Richmond, Dr. David Satcher, and Dr. C. Everett Koop. Unfortunately, the Bush administration has shelved this report, and this Congress has not held a single hearing to discuss or review its recommendations.

This week, New York City announced its smoking rates have dropped 11 percent in just 1 year as a result of Mayor Bloomberg's aggressive anti-tobacco policies, saving an estimated 30,000 lives. The response to this news should be obvious. The President and congressional leaders should pursue how to replicate these achievements across the country. But don't hold your breath. The National Republican Party is so closely aligned with the tobacco industry that the only hearings we have had on tobacco in the House recently have highlighted the alleged health benefits of smokeless tobacco, unbelievable as that is. That's the only hearing that has been held on the topic of tobacco.

Today's hearing will focus on the challenges facing clinical research in cancer. Let me mention two issues at the outset. First, to find cures for cancer we must adequately support a clinical research infrastructure that can prove that cures work. I'm very concerned that Dr. Robert Comis, a senior oncologist who represents the Cooperative Groups program, will testify today that current finding stifles innovation; destabilizes key functions such as our tissue banks, data management, and informatics platforms; and acts as a disincentive to both academic and community physician participation in research. That's because of these current funding levels. Now that reductions in reimbursement for oncologists man-

dated by Congress are due to take effect, it is critical that NCI and Congress assure adequate funding for research.

Second, to provide access to clinical trials, it is important that Government resources such as www.clinicaltrials.gov work well. This is a Web site created by the Congress in 1997 that is supposed to contain information for patients about ongoing trials for serious and life-threatening disease such as cancer. A 2003 study by the FDA staff found that fewer than half of the cancer studies that are legally required to be listed on this Web site were actually listed by the companies. This lack of participation by the drug industry in an important resource for patients is inexcusable, and I'm disappointed that the PHRMAceutical Research and Manufacturers Association, PHRMA, which was invited to testify, has been unable to send a witness to this hearing.

Today we will hear from leading health officials at the National Cancer Institute and the Food and Drug Administration, from senior cancer researchers, and from a leading representative of cancer patients. I thank these distinguished witnesses for coming today. I look forward to their testimony.

[The prepared statement of Hon. Henry A. Waxman follows:]

Opening Statement of
Rep. Henry A. Waxman, Ranking Minority Member
Committee on Government Reform
"Harnessing Science: Advancing Care by
Accelerating the Rate of Cancer Clinical Trial Participation"
May 13, 2004

Thank you, Mr. Chairman. I am pleased to participate in this hearing on how to accelerate progress against cancer. This is a topic that I have worked on for many years. When I was the chair of the health subcommittee of the Energy & Commerce Committee, I was responsible for legislation re-authorizing the National Cancer Institute. We worked with experts inside and outside of government to improve rehabilitation services, expand research on reproductive cancers, and strengthen education and grant-making programs.

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Today, we will hear from leading health officials at the National Cancer Institute and the Food and Drug Administration, from senior cancer researchers, and from a leading representative of cancer patients. I thank these distinguished witnesses for coming today, and I look forward to their testimony.

Chairman TOM DAVIS. Thank you very much. Do any other Members wish to make statements? If not, any statements can be put in the record.

Mr. Murphy.

Mr. MURPHY. Sure.

Chairman TOM DAVIS. The gentleman is recognized.

Mr. MURPHY. Mr. Chairman, thank you for holding this hearing on cancer screening trials. We all know few issues have as negative an impact upon so many as cancer. Though all of us have not been diagnosed, we certainly all hold the roots of this disease and we all know someone close to us who has or has had some impact of cancer.

While modern medicine has brought us a long way toward winning this battle, anyone who has a parent or child or friend diagnosed with cancer knows all too well we have not come anywhere near far enough. Increased participation in cancer clinical trials would significantly increase the discovery of newer cancer treatments with the ability to keep cancer patients feeling better while undergoing treatment, add years to their lives, and even cure them of the disease altogether; however, we will never have enough adult volunteers if patients continue to be misinformed or not encouraged to participate.

It is certainly sad to me to read the survey cited that the National Cancer Institute revealed that 85 percent of cancer patients are either unaware or unsure of participation in clinical trials is an option, and of the few who are aware of the trials, most of these individuals believe clinical trial treatment would be less effective than standard care, or that their insurance would not cover the cost, so something has to be done to change the public's perception of these trials.

I know in southwestern Pennsylvania the University of Pittsburgh Medical Center has received two grants to study these barriers and improve minority participation in clinical trials. This grant money is being used to essentially bring the trials to the patient through the utilization of teleconferencing, video equipment in outlying hospitals, providing modes of transportation to bring patients to trials and treatment, and working with other cancer centers and hospitals outside of the University of Pittsburgh Medical Center system.

Improving access and public perception of cancer clinical trials may seem to be an overwhelming task, but the doctors in my District are committed and excited about the cause.

I'm looking forward to the witnesses' testimony on the various steps groups are voluntarily taking to achieve higher rates of participation, as well as some of the problems they are confronting in their efforts.

In addition, I appreciate the committee's efforts to raise national awareness of this issue crucial to the future of medical innovation.

Thank you, Mr. Chairman.

[The prepared statement of Hon. Tim Murphy follows:]

Prepared statement for Congressman Murphy

Mr. Chairman, thank you for holding this vitally important hearing on cancer clinical trials.

Few issues have had as negative an impact on so many lives as cancer. Though not all of us have been diagnosed with cancer, we probably all know someone close to us who has and we are all aware of the devastating impact cancer can have on our lives and the lives of our loved ones.

While modern medicine has brought us a long way toward winning this battle, anyone who has had a parent, a child or a friend diagnosed with cancer knows all too well that we have not come anywhere near far enough.

Increased participation in cancer clinical trials would significantly increase the discovery of newer cancer treatments with the ability to keep cancer patients feeling better while undergoing treatment, add years to their lives and perhaps even cure them of the disease altogether.
However, we will never have enough adult volunteers if patients continue to be misinformed or not encouraged to participate.

It saddens me to read the survey cited by the National Cancer Institute revealing that 85% of cancer patients are either unaware or unsure if participation in clinical trials is an option. Of the few who were aware of the trials, most of these individuals believed clinical trial treatment would be less effective than standard care or that their insurance would not cover the costs.

Something must be done to change the public's perception of these life-saving trials.

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Chairman TOM DAVIS. Thank you very much.

The gentlelady from California, Ms. Watson?

Ms. WATSON. I, too, want to add my thanks to you, Mr. Chair, for bringing this issue up. I'm sure that Congressman Waxman will remember that way back in the 1980's a group of us got together in the California Legislature, a group of females, when we found that the only cancer testing was done on males, and breast cancer was coming more into high profile.

My statement ends up this way: when you are making good public policy, it takes years because you have to educate. So I thank you for gathering the witnesses here that will educate us to let us know that clinical trials are a must if we are going to make a dent in cancer.

Thank you, Mr. Chairman.

Chairman TOM DAVIS. Thank you very much.

We have a great selection of witnesses today. In our first panel we have Dr. Michaele Christian of the National Cancer Institute, along with Dr. Richard Pazdur from the Food and Drug Administration. They are going to provide the committee with an overview of the Federal Government's role in cancer clinical trials and highlight efforts the Government is taking to increase participation in clinical trials.

It is the policy of the committee that we swear all witnesses, so just rise with me and raise your right hands.

[Witnesses sworn.]

Chairman TOM DAVIS. Thank you very much. We are very privileged to have both of you here today. Your entire testimony is a part of the record and has been read, and what I'd like to do is we have some lights that will be in front of you. The green light goes on for 4 minutes, then you get an orange light for a minute, and then red is the end of 5. Try to sum up, and then we can move right to questions. Your entire statement is in the record.

Dr. Christian, we will start with you and then to Dr. Pazdur. Thanks for being with us.

STATEMENTS OF DR. MICHAELE CHRISTIAN, ASSOCIATE DIRECTOR, DIVISION OF CANCER TREATMENT AND DIAGNOSIS, CANCER THERAPY EVALUATION PROGRAM, NATIONAL CANCER INSTITUTE; AND DR. RICHARD PAZDUR, DIRECTOR, DIVISION OF ONCOLOGY DRUG PRODUCTS, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY DR. PATRICIA KEEGAN, DIRECTOR OF THE DIVISION OF THERAPEUTIC BIOLOGICAL PRODUCTS

Dr. CHRISTIAN. Good morning. Thank you Mr. Chairman, Representative Waxman, and Members for the opportunity to discuss NCI's efforts to deliver innovative and effective cancer treatments to the public.

I am Michaele Chamblee Christian, a medical oncologist and associate director of the Division of Cancer Treatment of the National Cancer Institute.

I have slides which are going to be hard to see, I think, on these screens, but you have hard copies. Cancer is actually more than 100 complex diseases and as depicted on this first slide, cancer

cells have many potential targets and pathways and processes that have been subverted by the malignant process. These differ in different patients and different tumor types, yet, because of our investment in basic research and advances in our understanding of biology, we now have a growing list of new agents and chemical entities in clinical trials and unprecedented opportunities to make significant progress in the treatment and prevention of cancer.

NCI funds an extensive clinical trial system, including over 3,000 clinical trial sites, more than 13,000 clinical investigators that accrue over 30,000 patients each year to trials. We study 138 investigational or experimental drugs. And this system has been very effective at developing the treatments and defining the standards of care for patients we treat today, and contributing to the fact that more patients with a diagnosis of cancer are living longer today.

We also have 88 formal clinical trials agreements within companies the biopharmaceutical industry, which is the source of most of the promising new agents in clinical development today.

Because of these extensive relationships, NCI is in a unique position to sponsor clinical trials of combinations of investigational agents owned by different companies. NCI has worked with over a dozen industry collaborators to arrange more than 20 trials of novel investigational combinations to date, and more are in development. Many of these regimens would not have been evaluated until one or more of the agents had received FDA marketing approval, potentially resulting in years of delay.

Why is this important? You have copies of the slides. We are going to try to do this without the slides. The cartoon that I was going to show you depicts one of the common problems and challenges with the targeted therapy of cancer, and that is that there are multiple branching and redundant signal pathways that control the behavior of cancer cells, and it is widely believed that many of the most promising new molecularly targeted agents will demonstrate their optimal utility in combinations that inhibit or modulate multiple targets in these critical pathways blocking progression of cancer, so we need to be able to give these simultaneously, and that's why these combinations are important.

I wanted to tell you about the components of the clinical trials program. There is an extensive early clinical trials program which is comprised of phase one and phase two clinical trials done via contracts and grants at academic centers. There are numerous translational research components that conduct the correlative of laboratory studies on blood and tumor specimens from patients so that in clinical trials we may learn not only whether a treatment works but how it works, so that we can select future patients better for treatment.

The map that you saw up there at one point represents the distribution of these clinical trial sites around the country and shows a very broad and I think good distribution of these sites.

The next slide should have been on Cooperative Groups funding, since funding for clinical trials is an issue, and points out that during the period from fiscal year 1998 to 2003 funding to the Cooperative Groups program increased by 62 percent.

NCI was asked to comment on why Cooperative Groups are not fully funded at the levels recommended by peer review, and I want-

ed to point out that the Cooperative Groups grants are amongst the largest in NCI's portfolio. In addition, each phase three trial that we sponsor costs anywhere from $2 million to $10 million, depending on its size. Our groups undergo peer review once every 6 years, where plans for the next 6 years are reviewed, along with the requested budget. However, this is a projected plan and a provisional budget because it is not possible to predict which clinical trials will actually be conducted 4 or 5 years in the future. So peer review recommendations are one component of effective coordination and stewardship that NCI staff consider in arriving at a funding plan.

In the next slide I wanted to show you that during this same period accrual to clinical trials also rose dramatically, by 24 percent in the phase three program and, importantly, by 58 percent, as shown in the light blue bars, in the early clinical trials program. That's important because that's where many of these promising new agents and combinations that will be evaluated in phase three trials are initially studied.

So my final slide just points out that there are a number of ongoing initiatives at NCI to broaden access to clinical trials for patients and to facilitate physician participation. The slide lists a number of them.

I wanted to just comment also in closing, that NCI is committed to effectively integrating its clinical trials mechanisms in order to make smarter use of the available resources and to ensure that we are optimally positioned to take advantage of emerging scientific and medical opportunities, speed accrual to the highest priority clinical trials, and accelerate the delivery of promising new approaches to cancer prevention and treatment to the American public.

I thank you for the opportunity to testify, and I will be happy to answer any questions.

Chairman TOM DAVIS. Thank you, Doctor.

[The prepared statement of Dr. Christian follows:]

Testimony
Before the Committee on Government Reform
United States House of Representatives

Delivering More Innovative and Effective Treatments to Make Cancer a More Treatable Disease

Statement of
Michaele Chamblee Christian, M.D.
Associate Director, Division of Cancer Treatment and Diagnosis, Cancer Evaluation Therapy Program
National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 10:00 am
Thursday, May 13, 2004

Good morning. I am Dr. Michaele Chamblee Christian, Associate Director of the Division of Cancer Treatment and Diagnosis for the Cancer Therapy Evaluation Program, in the National Cancer Institute (NCI), within the National Institutes of Health (NIH) and the Department of Health and Human Services. I am a medical oncologist.

Thank you, Mr. Chairman, Representative Waxman, and distinguished Members of the Committee, for the opportunity to discuss NCI's efforts to deliver innovative and effective cancer treatments to the public and the steps being taken to turn cancer into a more treatable disease.

Recent advances across the biomedical research enterprise have set the stage for unparalleled progress in biomedicine early in the 21st century. Basic research has given us an understanding that cancer is a disease process where normal cells are transformed into cancer cells through a series of defined steps that begin with small changes in cellular DNA. If left unchecked, these transformed cells can progress and spread to cause the suffering and death that we recognize as the horrible burden of cancer. Fortunately, our growing understanding of this disease process has revealed multiple opportunities to intervene.

New intervention strategies include preventing initiation of the disease process; early detection, when the disease is most amenable to elimination; and arresting the process to stop the spread (metastasis) of the disease, which is the primary reason that patients suffer unduly and die. In short, we are rapidly learning how to modulate the cancer disease process. This ability to intervene will ultimately eliminate some cancers and transform others into chronic, manageable diseases that patients do live with and not die from.

Scientific advances in genomics, nanotechnology, proteomics, immunology and bioinformatics may soon allow us to profile a patient's genetic, lifestyle, and environmental risk for cancer and to be able to combine effective prevention and early intervention strategies for those at high risk. For example, genomic analysis of a patient's tumor and proteomic patterns obtained from a patient's serum, as well as sophisticated imaging technologies designed for molecular detection, will be used to identify cancers at the earliest stages. Precise molecular diagnosis and patient-specific profiling will allow physicians to predict responses to specific interventions and provide a rational basis for tailoring treatments. The result will be more effective and less toxic, targeted agents delivered to patients, which will greatly change the outcome of many cancers and which is attainable in the foreseeable future.

Given these extraordinary opportunities, the NCI is focused on accelerating the pace of therapeutics development through better integration of its translational research and clinical trials components and better collaboration with our partners in academia, the community, the pharmaceutical industry, and other federal agencies to ensure that we are optimally positioned to address the most compelling scientific and medical challenges facing patients with cancer.

Bringing Innovative Treatments to the Public

The National Cancer Institute (NCI) has an extensive clinical trials program that is dedicated to developing more effective treatments for cancer patients using novel investigational (experimental) agents and new applications of commercially available drugs. In fact, the NCI is the largest sponsor of cancer clinical trials in the world and works extensively with the biotechnology and pharmaceutical industries, that are the source of many of these new agents, to accelerate the pace and scope of development. At any given time, the NCI has over 500 clinical trials actively enrolling patients and several hundred more still in analysis. Over 31,000 patients are enrolled on NCI-sponsored treatment trials each year, and many additional patients participate in clinical trials at NCI funded cancer centers across the country and in clinical trials sponsored by biopharmaceutical companies. Nearly 18,000 patients participate in NCI-sponsored cancer prevention and control studies. NCI treatment trials alone involve 3,300 clinical sites and approximately 11,000 investigators.

NCI has many initiatives underway to involve local healthcare providers, both at academic centers and in community practice settings, in clinical trials to allow patients everywhere to participate in the development of innovative treatments. Beginning in 1999, the NCI undertook two important pilot projects designed to increase both the speed of accrual and overall access to its large, phase 3 treatment trials. Phase 3 trials are, in large part, performed by the NCI's Clinical Cooperative Groups. Before 1999, the Groups had traditionally limited participation in their trials to their own membership. In a pilot project, the Cancer Trials Support Unit (CTSU) was created to open the trials of the 8 Adult Cooperative Groups to participation by any NCI-registered physician,

whether or not they were members of the Cooperative Group leading the trial. In order to make this a practical reality, and not overburden investigators with regulatory and audit requirements related to participation in trials led by different organizations, the CTSU consolidated the regulatory and data management activities for all the Cooperative Groups. This allowed the CTSU to provide access to the majority of the Group's Phase 3 trials in a consistent and uniform format. The CTSU now provides all Group members access to any of the Group's trials, thereby adding flexibility and access to the NCI system that did not formerly exist. To spur even greater participation in NCI-sponsored trials, since 2002 the CTSU has permitted physicians not affiliated with any Group to join and provide access to all trials on the CTSU menu to their patients.

This new approach to participation in trials via the CTSU has required substantial changes on the part of investigators and their staffs, reflected in the use of new informatics systems and in new management processes. There is growing evidence that this new approach is achieving its goals. Enrollment via this mechanism has steadily increased over the past 2 years and approximately 350 patients are currently being entered each month by this CTSU mechanism. In addition, the potential now exists for regulatory and many administrative documents for all Group trials to be handled exclusively by the CTSU. NCI would like to expand this effort by adding more trials to the CTSU menu and providing more efficient, automated systems (online registration and data management) to facilitate enrollments. This approach allows NCI to make its most important treatment trials widely available to patients across the country treated by experienced physicians in any setting, whether academic-centered or community-based, and regardless of their oncologist's affiliations.

A second pilot project, termed the Central Institutional Review Board (CIRB), was developed by NCI in direct response to repeated requests from the investigator community. Cumbersome and time consuming paperwork and IRB review process for clinical trials had to be completed separately at each of many hundreds of sites, even though many smaller sites might enroll only 1-2 patients on a trial, particularly for less common cancers (like Gastrointestinal Stromal Tumor [GIST]). The burden posed by local IRB review was frequently cited by investigators as a major reason for limited participation in clinical trials. While there can be no substitute for local IRB review for research being performed at a single institution, the CIRB primarily reviews large, Phase 3 studies performed at hundreds of sites across the country. By assuming the primary responsibility for review, adverse event monitoring, and follow-up paperwork for these national protocols, the investigators and local IRBs are spared duplicative application and review work and the process of gaining approval to enroll the first patient on a trial can be reduced from many weeks to as little as one to several days. This initiative has made important strides since its inception in 2000 and now consists of over 165 participating IRBs. The NCI has developed this project in close consultation with the HHS Office for Human Research Protections (OHRP). The CIRB members who perform the reviews are highly qualified oncologists, statisticians, patient/consumer advocates, pharmacists and nurses from across the United States who have volunteered to assist NCI by performing this task. While a formal evaluation of progress to date is currently underway, NCI hopes to expand the initiative this year to include 500 sites and, at the request of the

Children's Oncology Group, has initiated the formation of a second Board that will focus on reviewing pediatric multi-center trials.

In addition, NCI has major initiatives to disseminate information about state of the art treatments into the community. For example, since 1999 NCI has supported the HMO Cancer Research Network (CRN), a consortium of eleven research organizations affiliated with integrated healthcare delivery systems located across the U.S. that provide healthcare to over 10 million members. The CRN is engaged in a wide variety of population-based cancer control research ranging from exploring factors related to cancer occurrence and prognosis to health system design issues related to optimizing the performance of cancer prevention and screening services, to assessing the impact of cancer treatment on the quality of life of cancer patients. During its first funding cycle (1999-2002), with targeted support from NCI, CRN investigated barriers and facilitating factors related to participation of CRN physicians and members in cancer clinical trials. The results of this study have been submitted for publication, and based on these results CRN is currently designing an intervention trial to test organizational methods to enhance participation in clinical trials at CRN institutions. At the urging of NCI, in its renewal application (2003-2006) CRN will initiate a series of "cancer diffusion studies" that will document the rate and determinants of the dissemination of evidence-based cancer treatments in the community care settings of the CRN healthcare delivery organizations.

Public/Private Partnerships to Enhance Clinical Trials

NCI is continually working to expand its role in public-private partnerships as more private-sector companies begin to develop anti-cancer drugs. Many of the most promising new agents to treat cancer now come from the research and development

efforts of the biotechnology/pharmaceutical industry. Over the past 10 years, the number of new agents being developed by industry has grown over threefold, from 124 to 395. The current status of working relationships between NCI and private industry is excellent. These collaborative relationships have resulted in many pharmaceutical agents that are highly effective in the treatment of cancers and precancers. The Cancer Therapy Evaluation Program of the NCI, which coordinates NCI's clinical treatment trials, has formal relationships with more than 60 biotechnology and pharmaceutical companies, including 34 Cooperative Research and Development Agreements (CRADAs), 54 Clinical Trials Agreements (CTAs), and 9 Clinical Supply Agreements (CSAs). Similar arrangements exist within the Division of Cancer Prevention, which has 26 CTAs and 37 Investigational New Drug Applications (INDs), and NCI's intramural research program, which also supports or conducts clinical trials. NCI staff work closely with these corporate collaborators to ensure that the most important medical and scientific questions are addressed in the collaborative development of these agents and that duplication is avoided. Companies are often narrowly focused on the development path most likely to result in FDA approval, which may involve a single cancer type. NCI can accelerate the pace of broader development substantially to explore the many other cancer settings where an agent may have potentially important uses. Examples include the collaboration between Novartis and NCI-supported researchers that led to the development of **Gleevec** as a remarkably effective treatment for chronic myelogenous leukemia and now also for gastrointestinal stromal tumors. NCI is sponsoring clinical trials with Gleevec in many other tumor types that express the relevant targets. Likewise, in an ongoing partnership with Genentech, NCI-supported clinical investigators are testing a promising molecularly

targeted drug, **Avastin**, in patients with a variety of different cancer types, including those with advanced colorectal cancer who were previously treated with chemotherapy alone. Through a collaborative relationship with Searle and Pfizer, Inc., researchers found that the arthritis drug **Celebrex** can reduce the number of pre-cancerous colon polyps in patients with familial adenomatous polyposis, an inherited syndrome that predisposes them to colon cancer. NCI is exploring this important lead in a number of clinical trials. These specific examples represent only a small fraction of the clinical trials that NCI is supporting this year and the many industry partnerships that are predominantly for non-marketed investigational agents.

Because of its extensive relationships with bio-pharmaceutical companies, NCI is in the unique position of being able to broker and sponsor studies of combinations of investigational agents owned by different companies. It is widely believed that many of the promising new molecularly targeted agents will demonstrate their optimal utility in combinations that inhibit or modulate multiple targets in critical cancer cell pathways. NCI has worked with over a dozen industry collaborators to arrange 22 trials of novel investigational combinations to date and has commitments for additional high-priority trials, some containing 3 or 4 novel agents. Without these collaborations, many of these regimens would not have been evaluated until one or more of the agents had received FDA marketing approval, potentially resulting in years of delay. NCI continues to seek opportunities to provide additional incentives for bio-pharmaceutical companies to collaborate in the development of promising new agents and to further accelerate therapeutics development in the public interest. NCI is carefully following the impact of

incentives such as the extension of exclusivity provided in the Best Pharmaceuticals For Children Act of 2002, as one example.

NCI/FDA Collaboration

For the past year, NCI has also been working aggressively with the Food and Drug Administration via the NCI/FDA Interagency Oncology Task Force (IOTF) to increase collaboration and eliminate impediments to accelerated therapeutics development. The formation of the IOTF was an important strategic step toward achieving NCI's challenge goal of eliminating suffering and death due to cancer by 2015; and the FDA's goals of increasing the availability and use of safe and effective treatments for cancer. The goal of the IOTF is to leverage the expertise and capabilities of both agencies in order to streamline and accelerate the overall development of diagnostic, preventive, and therapeutic interventions for cancer.

Since its formation, the members of IOTF have identified several specific initiatives that are directed toward optimizing drug and device development. The NCI is working to specifically gather and synthesize the scientific support needed by the FDA to address specific regulatory issues. The IOTF is working through a series of specific subcommittees that are actively engaged in the following areas:

- Joint Training and Fellowships: The IOTF is focused on significantly increasing the number and quality of training of physicians and scientists that are expert in clinical research, the clinical approval process, and the translation of laboratory science into new products for cancer. To that end, the IOTF Training Subgroup has developed a series of fellowship programs that will allow NCI fellows to train at the FDA and has established fellowships for personnel from both agencies to

train in areas such as oncology product research for cancer detection, treatment, and prevention. These programs will be initiated in 2004.

- Developing Markers of Clinical Benefit: Work in this critical area includes the use of imaging in oncology drug development, collaborative development of the scientific data needed to establish surrogate endpoints for cancer clinical trials, and the potential utilization of advanced technologies such as genomics, proteomics, nanotechnology and immune monitoring to speed drug discovery and development, especially the regulatory phases. The subcommittee is organizing background materials to capture the state-of-the-science in specific types of cancer and technologies. These projects are all underway and will engage scientific input through publications, meetings, and workshops.
- Common Bioinformatics Platforms: NCI has recently launched a pilot program to connect the cancer research community through a new bioinformatics platform known as the Cancer Bio-informatics Grid (caBIG). One of the primary goals of this unprecedented effort is to improve the organization and reporting of data derived from oncology clinical trials. Among other projects, the NCI and the FDA are collaborating through the IOTF to utilize this common infrastructure to implement electronic INDs. As part of their participation in caBIG and the IOTF, the two agencies will pursue the development of standards to support the submission of clinical data and other electronic filings to shorten the time frame for processing and alleviate investigator workloads.
- Process Improvement: The IOTF has undertaken a series of projects to address specific issues or barriers that arise in the regulatory processes of oncology drug

development. These projects range from preclinical development through the range of clinical trials required for drug approval. Among the notable accomplishments are: the development of an NCI-FDA leadership group that can act to address questions from NCI-supported investigators during any phase of the regulatory review process; scientifically driven review of the preclinical requirements for IND filings; and the development of a more consistent process for the review of cancer prevention agents.

The IOTF meets regularly and actively addresses issues that can ultimately speed the development of new interventions for cancer. The IOTF subcommittees are currently framing new issues and developing resource materials that will facilitate investigators in preparing the data needed for the regulatory processes. In some cases, the FDA has already responded with guidance documents (such as a recent guidance on pharmacogenomics) and process changes, and the NCI is actively working to develop and synthesize the science needed to make regulatory decisions.

NCI Partnerships with Academic Health Centers and Cancer Centers

Because funding and sponsoring cancer research is fundamental to NCI's mission, there are extensive collaborations with cancer centers and academic health centers, both in drug discovery and development. NCI's Rapid Access to Intervention Development (RAID) Program is an example of a partnership with academia to accelerate the development of the most promising new agents from academic laboratories by providing the pre-clinical resources, such as drug formulation and toxicology studies, that often present significant obstacles to university laboratories that do not have the resources typically present in pharmaceutical companies. To date, **91** new agents have received

pre-clinical support through this program and many have entered clinical trials. The Division of Cancer Prevention has a similar program called RAPID (Rapid Access to Prevention Intervention Development) that has an additional 26 projects.

NCI has expanded its established working relationships with academic health centers and cancer centers to accommodate the increasing need for collaboration with laboratory scientists in conducting clinical trials for molecularly targeted agents. The cellular pathways and interactions involved in these molecular targets are extraordinarily complex and interrelated. These complexities require scientists to develop new techniques and tests to identify patients whose tumors contain the relevant targets and to monitor drug effects during treatment. More than half of NCI-sponsored cancer treatment trials initiated over the last 2 years have included correlative studies with laboratory scientists, and this trend is being seen increasingly in cancer prevention trials.

Clinical trials and much of the translational research that accompanies them are carried out in a variety of specialized mechanisms including: 1) **25** early therapeutics development contracts and cooperative agreements for Phase 1 and 2 trials, which are overwhelmingly based in cancer centers; 2) **56** Specialized Programs of Research Excellence (SPOREs), of which all but 3 are in cancer centers; 3) highly specialized disease specific consortia such as the AIDS Malignancy Consortium, and brain tumor consortia are located in cancer centers and academic health centers; 4) the 9 Cancer Cooperative Groups that conduct almost all Phase 3 trials and the pilot trials leading to them. The Groups are extensive national networks that include cancer centers and community sites. There are 9 adult national cooperative groups including 4 multi-specialty/multi-modality groups, 2 surgical groups, 1 each in gynecologic oncology,

radiation oncology and a diagnostic imaging group, as well as the Children's Oncology Group. Most cancer centers belong to several or many cooperative groups; 5) and the Community Clinical Oncology Program (CCOP), a large network of community oncology practices that conducts cancer treatment, prevention and control research and is not based primarily in academic centers, though the coordinating research bases are cancer centers. The CCOP program has grown rapidly over the past 10-15 years and now includes 61 individual grants to community based clinical trials research organizations in 39 states, Washington, D.C., and Puerto Rico. CCOP accrual has risen steadily over the past 10 years as a percentage of all Cooperative Group accrual and accounts for about 30% of accrual to treatment trials.

There is extensive involvement of cancer centers and academic health centers in most clinical trials mechanisms and in other activities supporting translational research, as described above. In an effort to accelerate clinical development and enhance collaboration and resource sharing, NCI is currently examining new approaches to integrating the clinical research that is conducted across these mechanisms to help ensure rapid and seamless progression of new agents and regimens through this process. A broadly representative Clinical Trials Working Group has been formed and includes senior NCI staff and external experts from across the clinical research spectrum, including academia, biopharmaceutical industry, and other federal agencies (FDA and the Center for Medicare and Medicaid Services) who will have an ongoing role in working together to improve the clinical trials process. The goal is to better integrate information, resources, and infrastructures so that the information gained in one venue is exploited most appropriately in the others. For example, when the basic research ongoing in an

NCI-designated cancer center or SPORE identifies a new molecular target in a specific disease, work can begin immediately on: identifying an assay to detect the target in tumor specimens from cancer patients; beginning clinical trials with agents that inhibit or modulate the target; and, on collecting tumor specimens from the patients on those or other clinical trials to further examine the impact of the target and its inhibition on the patient's tumor. Studies can also be initiated to examine the potential of new imaging techniques to identify these target effects non-invasively and to begin new pre-clinical studies of the targeted agents with other treatment approaches. One major aim of the NCI's current efforts to enhance cancer clinical research is to make many of these research processes, which have been sequential in the past, and proceed concurrently, thus enhancing the timeliness of the translation of new laboratory findings into clinical trials.

Rates of Participation in Clinical Trials

NCI was asked to comment about the differences in adult (about 3% of newly diagnosed cancer patients) and pediatric (about 60%) participation rates in cancer clinical trials. The rate of enrollment of children with cancer into clinical trials obviously far exceeds that for adults with cancer, although the absolute numbers of adults participating in trials is far higher. Most children with cancer are treated in tertiary care centers, the majority of which are associated with medical schools, whereas the vast majority of adult cancer patients are treated in community practice settings. The higher priority that academia places on research compared to the community setting facilitates the enrollment of children with cancer into clinical trials. Another important factor is the culture of the pediatric oncology discipline. This culture is driven by a history of progressive

improvements in childhood cancer outcomes that has reinforced in these specialists the belief that the best way to identify more effective treatments is through well-designed clinical trials. A key characteristic of the pediatric oncology culture is the willingness of researchers to collaborate in conducting multi-institutional clinical trials, which are essential since few single institutions see sufficient children with cancer to conduct the clinical trials that are needed to reliably identify more effective therapies. The remarkable efficacy of many pediatric cancer treatments and the dramatic progress that has been achieved by application of the pediatric oncology paradigm has created incentives for childhood cancer researchers to maintain their high rates of participation in clinical trials in the hope of continuing progress into the future. Because adult patients are predominantly treated in the highly competitive community setting, NCI has focused its attention and resources on building a far-reaching clinical trials infrastructure that is user-friendly for community physicians.

Educating the Oncology Community and Patients about Clinical Trials

Since the NCI introduced its Clinical Trials Education Series (CTES) in 2002, the NCI's Cancer Information Service (CIS) staff has been training health professionals and community organizations in how to use this excellent resource to educate patients and community groups about clinical trials. To increase awareness and education about clinical trials to the public and special populations, the CIS works in partnership with local, state, and federal agencies to expand the reach of NCI programs and services. The CIS Partnership Program strives to increase partners' awareness that cancer is a major public health problem and that the burden of cancer falls disproportionately on certain racial, ethnic, and socioeconomic groups. The CIS forms partnerships with organizations

to deliver information that motivates people to improve their health and connects partner organizations working in clinical trials education and outreach to build the capacity of those organizations in order to further the reach of their programs and services. Leukemia and Lymphoma Society chapters across the U.S. and NCI grantees known as the Special Populations Networks (SPNs) have been active participants in clinical trials education by involvement in train-the-trainer sessions offered by the CIS to become familiar with the CTES materials so that they can use the materials to inform their communities. The purpose of the SPNs is to build relationships between large research institutions and community-based programs and find ways of addressing important questions about the burden of cancer in minority communities. In particular, the SPNs and the CIS collaborate to increase awareness of and accrual to clinical trials.

The NCI's Cancer Information Service interacts directly with cancer patients and their families through its toll free number (1-800-4-CANCER), through the Internet using real-time instant messaging technology (*LiveHelp* in NCI's web site cancer.gov), and by e-mail (through NCI's Web site, http://www.cancer.gov). One of the most common reasons that patients, their families, and health professionals contact the CIS is for information about clinical trials. When appropriate, CIS proactively offers information on clinical trials to individuals seeking information on treatment options and conducts a customized search of NCI's database of clinical trials. The clinical trials search is provided directly to the patient so that they can discuss the trials with their physician. Accompanying clinical trials patient education booklets and materials are also offered to the individual.

The NCI also provides extensive internet access to information. The NCI's Web site (http://www.cancer.gov) provides the public with access to the PDQ database, consisting of cancer treatment summaries and cancer clinical trials, including approximately 2,000 cancer clinical trials open to patient accrual. These include trials sponsored by NCI, as well as those submitted by the pharmaceutical industry. The information summaries are developed through peer review and application of levels of evidence. A parallel summary is written for the lay public; both the health professional and patient versions are also available in Spanish. This registry is easily accessed through NCI's Web site, where users are able to narrow their search based on multiple parameters, including disease characteristics and geographic location. The Web site provides contextual material about clinical trial participation, to help users easily find information to help them make informed decisions regarding cancer treatment. The Web site is currently being redesigned to make it even easier for the public to find the information they need, including easier access to information regarding cancer treatment and clinical trials.

Improving the Clinical Trial Process

The Clinical Trials Working Group (CTWG) will attempt to better integrate the many diverse components of NCI's vast clinical trials program to ensure that the most important scientific questions are being addressed expeditiously, that duplication is avoided, resources are optimally distributed, and the structures in place are appropriate for 21st century science and technology.

Regarding increasing funding for the clinical trial cooperative groups to levels approved by peer review, it is important to note that the total funding for the cooperative groups rose by over 60% during the period FY98-03 to peer-review-recommended full funding

at that time, and the amount of funding to cover the costs associated with enrolling a patient in a trial more than doubled from less than $1000 at most sites to $2000 at all sites currently. The cooperative groups, albeit extremely important, are only one component of the complex clinical trials system described above. While they are responsible for accrual to crucial definitive Phase 3 studies which enroll the largest number of patients overall, they are also the largest individual grants in NCI's portfolio. The Clinical Trials Groups undergo peer review once every 6 years. At this review, both major accomplishments of the past 6 years and general scientific plans for the next 6 years are presented along with a budget to support these planned efforts. However, the specific number of clinical trials that will actually be conducted is not predictable, nor is the size of each trial or its accrual rate known at the time of peer review. Since these two factors are critical determinants of the funding, administrative support, and resources required to complete the research agenda, the annual budget of each Group fluctuates. Each Phase 3 trial costs anywhere from $2 million to $10 million, depending on its size. Therefore, the budget approved at the time of peer review is seen as a future projection based on an optimal set of provisional plans. Not all these plans will come to fruition for multiple reasons – some are duplicative of other efforts not known to peer reviewers at the time or review, and, not infrequently, unanticipated scientific developments and opportunities occur. Therefore, on an annual basis, NCI staff assesses the actual needs of each Group, prioritizes studies among the various Cooperative Groups, and allocates funds to each Group based on the total pool of available resources. While peer review does a good job of assessing the infrastructure and track record for these large cooperative groups, it is not able to assess the relative merits and prioritization of all of a group's proposed

research projects against the available NCI resources. NCI staff attempt to look across all the existing projects, research priorities, and proposed projects to make that assessment. The CTWG will enhance that process by suggesting areas where resources can be conserved and re-aligned to get the highest priority research done most efficiently, thereby accelerating the delivery of promising new treatments to patients.

The Role of www.clinicaltrials.gov

In 2000, the National Library of Medicine (NLM) launched a new Web site, www.clinicaltrials.gov, which aims to be a complete listing of all U.S. Government- and industry-sponsored clinical trials, including cancer trials. The NIH, through the NLM, has developed this site in collaboration with the Food and Drug Administration (FDA) as a result of the FDA Modernization Act, which was passed into law in November 1997. Although no single resource lists every cancer clinical trial being conducted in the United States and abroad, ClinicalTrials.gov currently contains approximately 10,200 clinical studies sponsored by the NIH, other federal agencies, and private industry.

Studies listed in the database are conducted in all 50 States and in over 90 countries. For each trial, the website presents a description of the purpose of the experimental trial, eligibility criteria for participation in the trial, location of the trial, and a point of contact for those who would like to enroll. ClinicalTrials.gov receives over 2.5 million page views per month and hosts approximately 16,000 visitors daily. In addition to helping patients find clinical trials in which they might participate, this website also educates users about clinical trials research, regulatory issues, and the meaning of informed consent. It provides links to background and related research and allows mining of statistics related to clinical studies.

NCI's cancer.gov website is a disease specific portal that includes extensive additional information about cancer, its prevention and treatment, and other material of interest to cancer patients and professionals, as described above. All clinical trials information in cancer.gov is downloaded to and available through www.clinicaltrials.gov as well.

NCI's Commitment to the 2015 'Challenge Goal'

The NCI is taking steps to achieve the 2015 challenge by accelerating the pace of progress across the entire cancer research continuum. Basic research, which is aimed at *discovering* the pathways that lead to cancer, represents the beginning of the continuum that proceeds through *development* of new agents and technologies and ultimately to the *delivery* of these new interventions to patients. Increasing our knowledge of the molecular defects in cancer cells and their microenvironment and identifying the biomarkers that characterize the cancer process will enable the development of new targeted interventions for preventing, detecting and treating cancer.

The NCI has identified six "mission-critical" research areas that offer significant potential for accelerating progress across the cancer continuum and for realizing our 2015 goal. These include: harnessing the power of the newly emerging science of molecular epidemiology to better identify risk populations; developing an integrative understanding of cancer (systems) biology to discover key biomarkers and targets; facilitating the development of strategic cancer interventions for targeted prevention, early detection, and treatment; creating a national integrated clinical trials system to more effectively test these interventions; overcoming health disparities to deliver these advances to those in greatest need; and developing a bioinformatics network to connect the cancer research

community and optimize the collection, analysis, and use of the enormous amount of data that must be managed and shared.

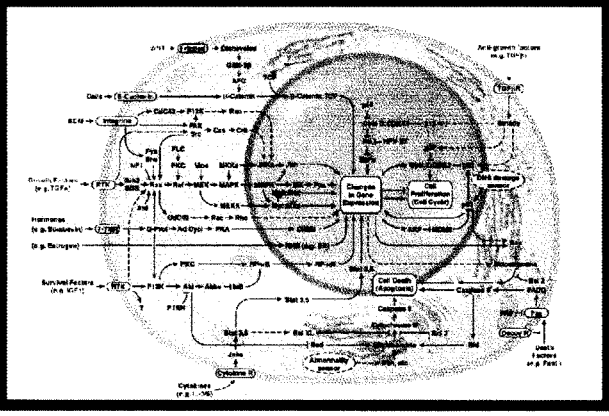
A key example of progress in a mission-critical area is NCI's launching of the Cancer Biomedical Informatics Grid (caBIG). This pilot initiative has the potential to transform the pace of cancer research by providing the tools needed to share information and data, by initially connecting 50 of our NCI-designated cancer centers through an NCI-developed open source system to become, in effect, the "World Wide Web" of cancer research. This platform eventually will link individual cancer researchers and research institutions across the nation, and around the world, in an open source, federated network that will enable researchers to share tools, standards, data, computing applications, and technologies. This bioinformatics initiative will allow researchers to answer research questions more rapidly and efficiently and will accelerate progress in all aspects of cancer research.

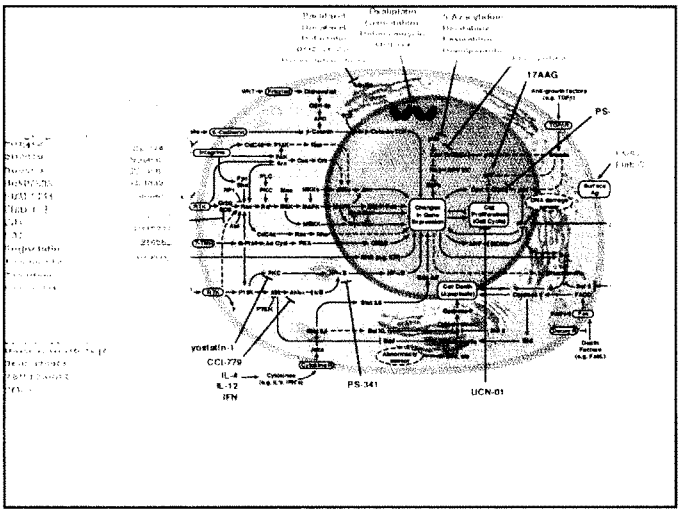
Conclusion

NCI-supported clinical trials provide a crucial infrastructure for moving new cancer interventions from the laboratory to studies in people with, or at risk for, cancer and then to the health care setting. These clinical trials have always included investigations of a broad set of interventions – chemoprevention, chemotherapy, radiation, and surgery – sometimes used alone and sometimes in combination. With recent advances in deciphering the molecular changes that cause cancer, a new paradigm of cancer treatment and prevention research is emerging and bringing with it the promise of an exponential growth in effective cancer interventions.

"Cancer" is >100 complex diseases

The Cancer Cell Has Many Potential Targets: Pathways Subverted in Cancers



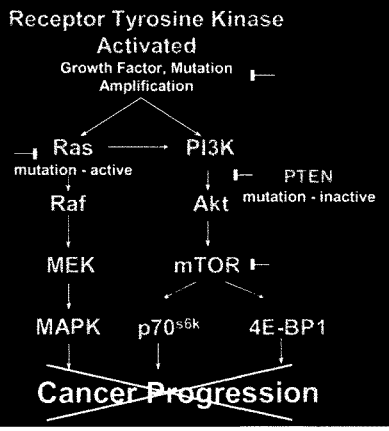


CANCER THERAPY EVALUATION PROGRAM – NCI
CLINICAL TRIALS PROGRAM IN TREATMENT 2003**

Scope of the Clinical Trials Program in Treatment

• Clinical Trials Sites	~3,300
• Clinical Trials Investigators* *registered at any time	12,869
• Clinical Trials Patient Accrual** **FY2002 data, 2003 is incomplete	30,057
• Investigational New Drug Applications	138
• Clinical Trials Agreements with industry	88

Targeting Signaling Pathways with Combinations



NCI-CTEP CLINICAL TRIALS PROGRAM IN TREATMENT

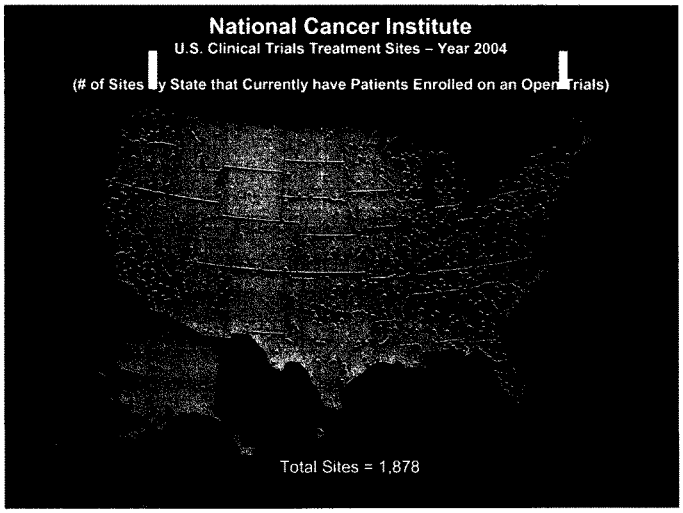
Early Clinical Trials Program

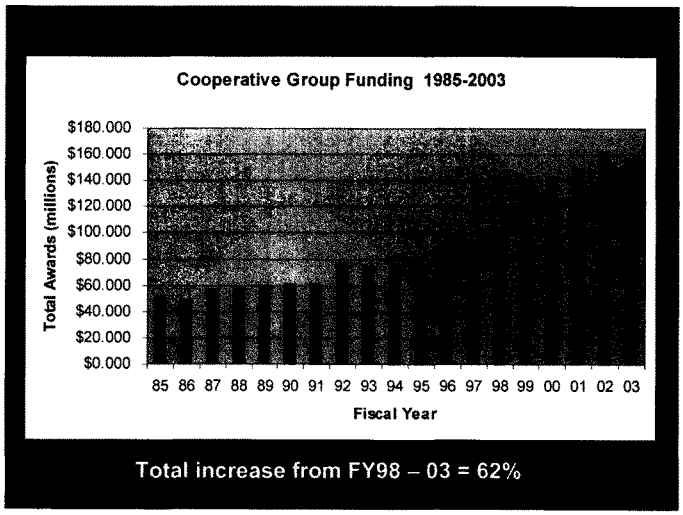
- o Phase 1/Phase 2 contracts & cooperative agreements
- o Translational Research Components
  - Translational Research Initiative
  - Specialized Programs of Research Excellence (SPORES)
  - Interdisciplinary Research Teams for Molecular Target Assessment

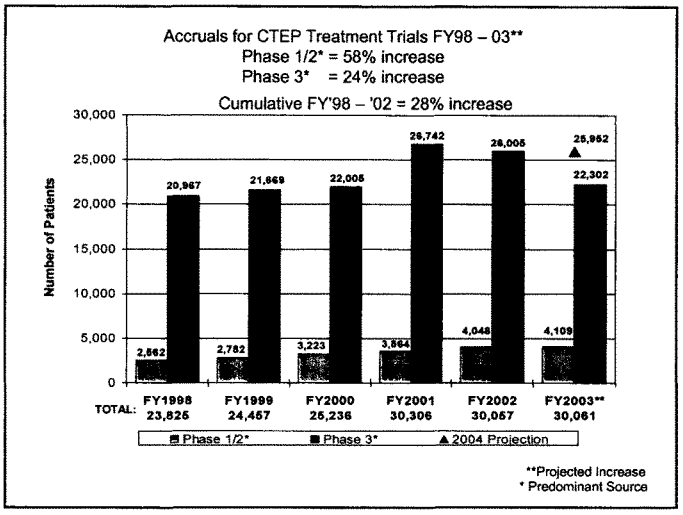
Phase 3 (Late) Clinical Trials Program

- o Clinical Trials Cooperative Groups
  - 8 adult + 1 pediatric
  - Multi-specialty/multi-modality national networks
- o Community Clinical Oncology Program (CCOPs)

Analogous Structures Exist In Cancer Prevention




Cooperative Group Funding 1985-2003
Total Awards (millions)
$180.000
$160.000
$140.000
$120.000
$100.000
$80.000
$60.000
$40.000
$20.000
$0.000
85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 00 01 02 03
Fiscal Year
Total increase from FY98 – 03 = 62%

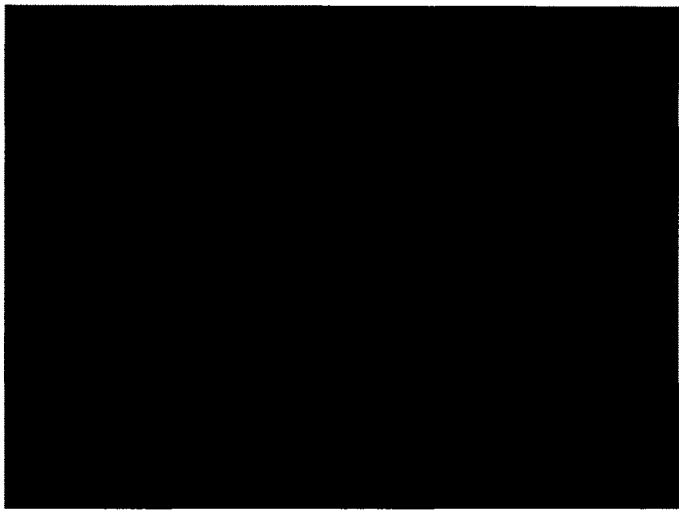

Accruals for CTEP Treatment Trials FY98 – 03**
Phase 1/2* = 58% increase
Phase 3* = 24% increase
Cumulative FY'98 – '02 = 28% increase
Number of Patients
30,000
25,000
20,000
15,000
10,000
5,000
0
20,967
21,869
22,005
26,742
26,005
25,952
22,302
2,562
2,782
3,223
3,864
4,048
4,109
TOTAL: FY1998 23,825
FY1999 24,457
FY2000 25,236
FY2001 30,306
FY2002 30,057
FY2003** 30,061
Phase 1/2*
Phase 3*
2004 Projection
**Projected Increase
* Predominant Source

NCI INITIATIVES TO SPEED ACCRUAL TO CLINICAL TRIALS

- Cancer.gov website
  - **extensive online directory of trials and information on cancer treatment**
- Cancer Information Service – **1-800-4-CANCER**
- Cancer Trials Support Unit
  - **provides centralized access to over 60 treatment trials**
- Central Institutional Review Board
  - **decreases administrative burden for investigators and sites**
- Community Clinical Oncology Program (CCOPs)
  - **expansion to more sites nationwide**

Special Populations Accrual Enhancements

- **Clinical Trials Outreach Units**
  - **1999: Howard University**
  - **2000: Meharry Medical College**
- **Minority Accrual Supplements**
  - **2001, 2002: supplements to 8-10 institutions**
- **Minority Based CCOPs**
- **Special Populations Networks**



Chairman TOM DAVIS. Dr. Pazdur, thanks for being with us.

Dr. PAZDUR. Mr. Chairman and members of the committee, I am Richard Pazdur, M.D., the Director of the Division of Oncology Drug Products at the Center for Drug Evaluation and Research at the Food and Drug Administration. Dr. Patricia Keegan, the Director of the Division of Therapeutic Biological Oncology Products at CDER, is accompanying me today to answer any questions on biological products.

I am pleased to be with you today to discuss what our agency is doing to accelerate the delivery of innovative cancer treatments to meet the needs of cancer patients and their families. FDA's mission is to ensure that new cancer drugs are safe and effective. We also facilitate access to promising therapies for seriously ill and dying patients when no other treatment is available.

Since the FDA last testified before this committee in June 2000, a number of important cancer drugs have been approved and are helping cancer patients. Of particular note are the number of innovative drugs that are targeted to specific parts of the cancer cells. These new therapies are a glimpse of the future of cancer therapy and should be a source of encouragement to the American public and to cancer patients and their families.

FDA has numerous programs in place to help speed the development and approval of promising drugs to cancer patients. Let me briefly mention some of these programs.

Under the accelerated approval route, FDA can approve drugs for serious or life-threatening conditions. These drugs demonstrate the potential to address unmet medical needs based on a surrogate end point that is "reasonably likely" to predict clinical benefit.

Second, priority review is intended to direct overall FDA review attention and resources to the evaluation of applications for products that have the potential for providing significant therapeutic advances.

Third, a drug sponsor may request fast track status. This designation facilitates the investigational development and the approval of drugs that provide significant advancements in the treatment of serious or life threatening diseases. These programs have been instrumental in shortening the time to approval for many promising cancer treatment drugs; however, the FDA is aware that there is growing concern that many of the new basic science discoveries made in recent years may not quickly yield more effective, affordable, and safe medical products for patients. This is because the current medical product development path is becoming increasingly challenging. During the last several years, the number of new drugs and biological applications submitted to the FDA has declined significantly. The number of innovative device applications has also decreased.

In response, on March 16, 2004, the FDA released a report entitled, "Advancing America's Health: Advancing Medical Breakthroughs." We refer to this FDA report as a critical path. This timely paper calls for academic researchers, product developers, and patient groups to work with the FDA to identify ways to modernize tools for speeding approval, innovative products to the market to improve public health.

The report provides FDA's analysis of the current pipeline problem, the recent slow down instead of the expected acceleration in innovative medical therapies reaching patients. FDA is planning an initiative that will identify and prioritize the most pressing development problems, and, second, the areas that provide the greatest opportunities for rapid development and public health benefits. This will be done for all three dimensions along the critical pathways, namely: safety assessment, evaluation of Maryland utility, and product industrialization. We will work together with stakeholders to identify the most important challenges.

Concurrently, FDA will refocus its internal efforts to ensure that we are working on the most important problems and intensify our support of key projects.

Thank you for the opportunity to discuss these important issues with you. I would be happy to answer any questions.

[The prepared statement of Dr. Pazdur follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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STATEMENT BY

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CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

"HARNESSING SCIENCE: ADVANCING CARE BY ACCELERATING THE RATE OF CANCER CLINICAL TRIAL PARTICIPATION"

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

U.S. HOUSE OF REPRESENTATIVES

May 13, 2004

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman, Members of the Committee, I am Richard Pazdur, M.D., the Director of the Division of Oncology Drug Products (the Division) at the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA or the Agency).
Dr. Patricia Keegan, the Director of the Division of Therapeutic Biological Oncology Products at CDER, is accompanying me today to answer questions on biological products. Prior to coming to FDA, I was associated with the M.D. Anderson Cancer Center in Houston, Texas, for 11 years, where I was involved in patient care, cancer research, medical education, and administration.

Because of my prior experience with patient, academic, and scientific communities, I am acutely aware of how FDA's decisions and requirements can impact the public we serve. Under the Federal Food, Drug, and Cosmetic (FD&C) Act, the Public Health Service Act, and related statutes, the government performs a vitally important role in helping to ensure that the medical products that patients and their health care practitioners rely upon are both safe and effective. These safeguards are particularly important for our most vulnerable citizens, those who are seriously ill.

I am pleased to share with you what our Agency is doing to accelerate the delivery of innovative cancer treatments to meet the needs of cancer patients and their families. Let me start by discussing the clinical trials required in FDA's new drug approval process and how patients gain access to these clinical trials. Our Division's mission within FDA is to ensure

that new cancer drugs are safe and effective and to facilitate access to promising therapies for seriously ill and dying patients when no other treatment is available. In my remarks, I will use the term "drug" to refer to both traditional small molecules and to therapeutic biological products.

Clinical Trials

Most clinical trials are carried out in steps called phases. Each phase is designed to gather different types of information. Patients may be eligible to participate in studies in different phases, depending on their general condition, the type and stage of their cancer, and what therapy, if any, they have already had. Patients are seen regularly by the investigators during the study to determine the effect of the treatment, and treatment is stopped if side effects become too severe.

The purpose of a Phase I clinical trial is to find the best way to administer a new treatment and learn how much of it can be given safely. In a Phase I study, a new treatment is given to a small number of patients. For a new drug, the study starts by giving a very low dose of the drug and the dose is then slowly increased as new patients enter the trial.

Phase II studies are designed to find out if a treatment has the intended effect. In the context of cancer therapy, Phase II studies are designed to study whether the treatment actually damages cancer cells or slows their growth in people. Usually groups of 20 to 50 patients with one type of cancer receive an investigational treatment in Phase II studies. For example, patients with breast cancer who no longer respond to standard therapy may choose to be treated in a Phase II study.

Patients are closely observed for anti-cancer effect by repeated measurement of tumor size to see if tumors have shrunk since the beginning of the trial.

Phase III studies usually compare a new treatment that appeared to have an effect in the small Phase II studies with standard (generally accepted) therapy, or compare the combination of the new therapy and standard therapy to standard therapy alone. Phase III trials require larger numbers of patients; some trials enroll hundreds or even thousands of patients. Patients are usually randomized (assigned by chance) to the treatments being studied. The group that receives the standard treatment is called the "control" group. The researchers expect that a certain number of these patients will be helped by the treatment.

Phase IV trials may be conducted after a drug has been approved. Companies often, for example, carry out studies of new drugs in patients with different tumors or with different stages of disease. FDA may also request, and the sponsor may agree to conduct, other post-marketing studies to provide additional data to improve the safe and effective use of the drug.

Patient Access to a Clinical Trial for Cancer Therapy

The access process starts with a drug sponsor seeking to develop a new cancer drug, which is usually a pharmaceutical company or a research scientist at a university or at the National Cancer Institute (NCI) at the National Institutes of Health (NIH). Before clinical testing begins, researchers analyze the drug's main physical and chemical properties in the laboratory and study its pharmacologic and toxic effects in laboratory animals. These are known as pre-clinical studies. If the laboratory and animal study results show promise, the sponsor submits

an investigational new drug (IND) application for FDA review prior to initiating testing in people.

Once FDA has reviewed the sponsor's IND and allowed it to proceed, it progresses subject to the oversight of the local Institutional Review Board (IRB). An IRB is a panel of scientists and non-scientists that oversees clinical research, and approves the protocol for clinical trials. Experienced clinical investigators give the drug to a small number of cancer patients who have no other available therapy. These phase I studies assess the most common acute adverse effects and examine the amount of drug that patients can take safely without unacceptable side effects. Initial clinical studies also begin to clarify what happens to a drug in the human body, how it is changed (metabolized), how much of it (or a metabolite) gets into the blood and various organs, how long it stays in the body, and how the body gets rid of the drug and its effects.

If Phase I studies do not reveal major problems, such as unacceptable toxicity, the next step is to conduct a clinical study in which the drug is given to patients who have medical conditions that may benefit from the potential cancer drugs. Several different types of cancers are often explored in these Phase II studies. Researchers then assess whether the drug has a favorable effect on the condition.

Testing experimental drugs in people inevitably presents ethical questions. For example, there have been discussions of when it is ethical to give some patients placebos. A general principle, agreed on internationally, is that patients in a study must not be denied known effective treatment that prevents death or serious injury. In cancer trials, patients are never

denied such treatment. Placebos may be used when there is no known effective treatment. In a so-called add-on study, when the new drug is added to standard treatment, it is typical for study participants to get the standard treatment in an unblinded way. Patients are then randomly assigned treatment with the new drug or a placebo in addition to the standard treatment.

FDA recommends that anyone interested in participating in a clinical trial discuss the idea with his or her physician. Doctors are generally aware of investigational drugs that might be of benefit to their patients and of clinical trials involving these drugs. Patients can obtain detailed information from a variety of sources, including drug sponsors, FDA (if the information is public), and NIH. In fact, industry-sponsored trials are statutorily required to be listed on *www.clinicaltrials.gov*.

Clinical trials are carried out at major medical research centers, at NIH, and even in doctors' offices. Although they often involve hospitalized patients, many clinical trials can be conducted on an outpatient basis, with participants more or less going about their normal activities. The center or institution where a study is to be carried out often runs newspaper advertisements recruiting potential participants for clinical studies that tell readers where to call or write for further information.

These aspects and other implications of taking part in a clinical trial must be fully explained in advance by the people conducting the trial, and patients must agree to the conditions before they can participate. The hope of personally benefiting from a new drug or the desire to take part in research that might one day benefit millions is what makes people volunteer for clinical

trials. It should not prevent them, however, from finding out all they can about being a part of the process. They must also understand that new treatments, although promising, may prove ineffective or harmful.

Trends in Cancer Drug Development and FDA Approvals

Since FDA last testified on this issue before this Committee in June 2000, a number of important cancer drugs have been approved and are helping cancer patients. Of particular interest in recent years are a number of drugs that are not the so-called cytotoxic agents (drugs that are broadly toxic to rapidly growing cells), but are more targeted to specific parts of cancer cells. A few of these drugs that have been approved and are successful for thousands of cancer patients include: Velcade for the treatment of multiple myeloma; Iressa for non-small cell lung cancer; Erbitux for refractory EFG-receptor expressing metastatic colon cancer; Avastin for initial treatment of metastatic colon cancer; Campath for treatment of refractory chronic lymphocytic leukemia; Bexxar and Zevalin for treatment of non-Hodgkin's lymphomas and Gleevec for pediatric and adult chronic myeloid leukemia (CML), and gastrointestinal stromal tumors (GIST).

Expediting Approval of Cancer Therapies

The Food and Drug Administration Modernization Act (FDAMA), enacted November 21, 1997, amended the FD&C Act relating to the regulation of food, drugs, devices, and biological products. With the passage of FDAMA, Congress enhanced FDA's mission in ways that recognized that the Agency would be operating in a 21st century characterized by increasing technological, trade, and public health complexities. Among other things, FDAMA codified

many of FDA's initiatives and existing programs designed to expedite drug development and expand access to unapproved therapies. All of these programs have been instrumental in shortening the time to marketing approval for cancer drugs and biologics. FDA programs codified in FDAMA include:

- **Expediting Approval of Cancer Drugs** – The FDA has shown a long-standing commitment to the prompt consideration and, when appropriate, early approval of new therapies for cancer patients. In 1996, the Agency launched its "Reinventing the Regulation of Cancer Drugs" initiative with the goal of accelerating the approval of and expanding patient access to cancer drugs. This program described how FDA's Accelerated Approval Rule or Subpart H Approval (21 CFR 314.510) would be used to approve cancer drugs earlier in their development and for expanded access programs (the treatment IND) to be used to make promising drugs broadly available prior to marketing.

    - **Accelerated Approval or Subpart H Approval** - Under the Accelerated Approval Rule subsequently incorporated into the Fast Track provision of FDAMA (section 112), FDA can approve treatments for serious or life-threatening conditions that demonstrate the potential to address unmet medical needs on the basis of a "surrogate endpoint" that is "reasonably likely" to predict clinical benefit. A surrogate endpoint is a measure of drug effect (e.g., tumor shrinkage) that does not by itself show a patient benefit, such as decreased pain or longer survival, but is thought likely to lead to such a benefit. Some surrogate endpoints are well established (blood pressure, for example) and are a routine basis for approval. Other surrogate endpoints are not as certain, and these may now be used under our Accelerated Approval authority. The reinvention program specifically declared that FDA would rely on tumor shrinkage in refractory cancer as a basis for approval, and we have regularly done so. Since 1996, four out of nine biological products were approved under accelerated approval, and many new drug approvals have been based on this study endpoint, allowing for earlier marketing than would have been possible had FDA waited for a documented effect on such an endpoint or survival. Under accelerated approval, the manufacturer commits to study the drug's actual clinical benefit after marketing.

    - **Expanded access**- Expanded access mechanisms are designed to make promising products available as early in the drug evaluation process as possible. Several other FDA procedures encourage or speed cancer drug development. Prior to drug approval, single patient and expanded access programs provided promising cancer drugs to patients with advanced cancer. Programs for patient use prior to drug approval include single-patient protocols, single-patient exemptions, protocols for treatment, and treatment INDs. Because of the large number of patients with metastatic lung cancer and limited therapeutic options available to patients with

progressive disease, over 20,000 patients received the drug, Iressa, prior to its approval through a protocol designed to provide patient access to this promising drug.

- **Priority Review**-When marketing applications are submitted they are designated as priority (P) or standard (S). Priority New Drug Applications (NDAs) and effectiveness supplements are those that could have important therapeutic impacts. A priority designation is intended to direct overall attention and resources to the evaluation of applications for products that have the potential for providing significant therapeutic advances. Specifically, FDA's goal is to review a priority NDA within 6 months rather than the standard review time of 10 months. Since 1996, 13 biologics (9 BLAs and 4 supplements) and 55 drugs (27 NDAs and 28 supplements) for cancer therapies have received priority review and approval.

- **Fast Track** refers to a process for interacting with FDA during drug development. The fast track programs are designed to facilitate the development of and expedite the review of new drugs and biologics to treat serious or life-threatening conditions that demonstrate the potential to address unmet medical needs. "Rolling Review" is allowed for certain applications that receive fast-track status. To provide clear information to industry regarding participation in the fast track process, FDA issued a guidance document on this provision in September 1998.

Fast-track designation for a clinical development program can occur at any time of the development process. It is initiated by the sponsor's request for designation and can be granted for any development program (as projected by the sponsor) that is intended to demonstrate that its drug/biologic will affect a serious or life-threatening disease or condition. This may be an improvement over existing therapy or treatment where no alternative therapy exists.

It is important to note that FDAMA did not alter FDA's effectiveness standard, except by giving explicit authority to the Agency to rely on data from a single, adequate and well-controlled clinical investigation and confirmatory evidence as support for approval in certain cases. Even for drugs intended for serious and fatal illnesses, there must be substantial evidence that the drug will have the effect it purports to have. As noted, however, the law

recognizes that the nature of the effect that needs to be demonstrated might vary depending on the urgency and clinical need.

Expanding Access to Cancer Therapies Approved in Other Countries

Part of the reinvention effort was to see whether there were useful drugs available in other countries, but not in the U.S. In 1996, FDA sent a letter to the regulatory authorities of 24 countries requesting a list of all cancer or cancer-related therapies approved in their country over the last 10 years. Detailed responses were received from 15 countries. In 1996, forty-four drug products not marketed in the U.S., but marketed in one or more of these countries, were identified. In 1998, the Agency completed its evaluation of the drugs identified as having been approved in foreign countries. Some of them were later approved in the U.S.; some are under review. The Agency concluded, however, that there did not appear to be significant differences in the spectrum of drug products available for the treatment of cancer in the U.S. and in foreign countries. There are no products that appear to potentially provide a significant benefit in cancer treatment that cannot be accessed by U.S. patients, either in the marketplace or through an established IND mechanism.

FDA is Working with Other Organizations to Increase Participation of Cancer Patients in Clinical Trials

Scientific experts from CDER routinely meet with representatives of scientific professional societies including the American Society of Clinical Oncology (ASCO) and the American Association for Cancer Research (AACR) as well as their counterparts from the NCI's extramural program. CDER and FDA's Center for Biologics Evaluation and Research (CBER) have developed workshops in conjunction with ASCO, AACR, and NCI, with

participation from academia, industry, and patient advocacy groups. As part of these workshops, the group has re-assessed clinical endpoints for approval of cancer therapeutics. Resulting from what was learned at the workshops, FDA issued formal guidance, as sought by its FDA's Oncologic Drugs Advisory Committee. Other similar workshops have been held over the last few years to address concerns regarding endpoint issues, including endpoints in lung cancer and in colon cancer. Further discussion of endpoints was addressed at subsequent advisory committee meetings. CDER and CBER experts are developing guidance documents on these topics.

FDA meets monthly with the NCI Cancer Therapy Evaluation Program (CTEP) to discuss issues in oncology drug development, including patient access, protocol design, and novel agents under development. Scientists from CDER and CBER's Oncology Divisions attend weekly protocol meetings conducted by NCI for review of NCI-funded trials and proposals for new trials. In addition, FDA sponsors visiting fellowships for medical oncology fellows from cancer centers and major universities.

FDA Office of Special Health Issues (OSHI)

FDA staff is aware of the frustrations that patients with life-threatening illnesses and their families experience when trying to obtain information about potentially helpful therapies, especially when there is no treatment for their disease. In addition to staff within FDA's medical product centers that routinely provide assistance and information to consumers, FDA, in 1988, created the Office of Special Health Issues with trained staff to work with patients with life-threatening diseases. The skilled staff of FDA's Office of Special Health Issues

works with patients with serious or life-threatening diseases such as AIDS, cancer, Parkinson's disease, or Alzheimer's disease, to name a few.

Patients usually call to obtain information about unapproved treatments currently being researched. Once our staff explains that FDA cannot disclose certain confidential information about drugs or devices that are not yet approved, we direct callers to listings of clinical trials where they can locate a trial for which they might be eligible.

We are able to talk with patients about any treatment that appears in a public access database, such as the *ClinicalTrials.gov* database operated by the National Library of Medicine or the National Cancer Institute's database at *http://cancertrials.nci.nih.gov* Our staff is working actively with the National Library of Medicine and the pharmaceutical industry to include more clinical trials in the *ClinicalTrials.gov* database. If a patient does not have a computer, a patient can access the NCI's clinical trials by calling 1-800-4-CANCER. An information specialist will search the database and send the trials information to the patient within 3 days.

Our goals in serving patients with life-threatening diseases and their family members are straightforward:

- Promptness (returning patients' and family members' calls within 24 hours);
- Accessibility (listening to the caller's concerns and giving the caller as much time as he or she needs);
- Education (about the drug approval process and his or her options); and
- Assistance (providing additional information to the patient or family member that may be helpful, e.g. other sources of information).

We estimate that we receive approximately 1,000 inquiries (phone and e-mail) from patients and family members annually.

During the past 16 years, FDA has made a substantial commitment to assist patients and consumers who wish to become more involved with the drug approval process. We have initiated two programs to integrate patient advocates into our regulatory process: the Patient Representative Program and the Cancer Drug Development Patient Consultant Program. The Patient Representative Program recruits and trains advocates to serve as advisors on FDA's advisory committees considering drugs to treat life-threatening diseases. Since the inception of the Patient Representative Program, over 100 patient representatives have participated in more than 70 advisory committee or panel meetings. Examples of disease areas that have had patient representatives are: AIDS, cancer, diabetes, Parkinson's, temporomandibular joint disorder, irritable bowel syndrome, congestive heart disease, hepatitis B and C, polio, sickle cell disease and lupus, and most recently, major depressive disorder. Patient representatives are appointed as special government employees and must adhere to conflict of interest and confidentiality regulations. We select the patient representatives from their disease advocacy communities, base the selection on specific entry criteria, and when selected, provide them training in preparation for participating in advisory committee meetings.

The Cancer Drug Development Patient Consultant Program involves patient advocates earlier in the drug development process. Cancer patient advocates serve as patient consultants in the pre-approval, clinical trial phase of cancer drug development. The patient consultant participates in FDA and drug sponsor meetings and provides advice to FDA and to the drug

sponsors on topics such as clinical trial design, endpoint determination, expanded access protocol development, and clinical trial patient recruitment strategies.

FDA's OSHI's staff is an access point for the organized patient advocacy community. Many patient advocacy organizations, in addition to providing valuable information to patients, are focused on understanding the specifics of drug approval such as drug labeling.

OSHI staff listens carefully to the patient advocacy community and encourages them to stay involved with FDA's regulatory and policy-making process. We maintain a mailing list of patient advocacy groups who represent the interests of patients with a variety of life-threatening diseases. We routinely notify them about FDA advisory committee meetings, open public hearings or seminars on research or policy and drug approvals, and other FDA issues of interest to patient advocates. Sometimes these small patient advocacy organizations are uncertain about how to approach FDA. The staff wants to be sure that uncertainty and inexperience with drug regulation does not prevent the advocate's voices from being heard. FDA staff believes that the thoughts and concerns of the patient advocacy community are valuable and must be integral to our decision-making process.

The NCI/FDA Interagency Oncology Task Force (IOTF)

The Interagency Oncology Task Force (IOTF) was formed early in 2003 by Dr. Andrew von Eschenbach, Director of the National Cancer Institute, and Dr. Mark McClellan, then Commissioner of Food and Drugs. The formation of the IOTF was an important strategic step toward achieving FDA's goal of increasing the availability and use of safe and effective

treatments for cancer, and NCI's challenge goal of eliminating suffering and death from cancer by 2015. The purpose of the IOTF is to leverage the expertise and capabilities of both agencies for the expressed purpose of streamlining and accelerating the overall development of diagnostic, preventive and therapeutic interventions for cancer.

Since its formation, the members of IOTF have collaboratively undertaken an analysis of the overall development and review process for new oncology drugs and devices and identified several specific initiatives that are directed toward optimizing drug and device development. NCI is working to specifically gather and synthesize the scientific support needed by FDA to address specific regulatory issues. FDA is working cooperatively with NCI to address important scientific issues including:

- Significantly increasing the numbers of physicians and scientists who are expert in clinical research, the clinical approval process and the translation of laboratory science into new products for cancer through high quality training,
- Developing markers of clinical benefit using imaging in oncology drug development, collaborative development of the scientific data needed to establish improved surrogate endpoints for cancer clinical trials, and the potential utilization of advanced technologies,
- Utilizing bio-informatics technology to expand the use of an electronic form of the IND application,
- Establishing an FDA-NCI subgroup to address questions from NCI-supported investigators during any phase of the regulatory review process,
- Enhancing scientifically driven review of the pre-clinical requirements for IND filings; and
- Developing the scientific base for consistent review of cancer prevention agents.

The IOTF is meeting regularly and actively addressing issues that can ultimately speed the development of new advanced interventions for cancer. The IOTF subcommittees are currently developing resource materials that will assist investigators in preparing the data needed for FDA's regulatory process. FDA has already responded with guidance documents (such as a recent guidance on pharmacogenomics) and process changes.

FDA's Critical Path Initiative

On March 16, 2004, FDA issued a report entitled, "Advancing America's Health; Advancing Medical Breakthroughs." This "Critical Path" paper calls for academic researchers, product developers, and patient groups to work with FDA to help identify opportunities to modernize tools for speeding approvable, innovative products to market to improve public health. The report provides FDA's analysis of the current pipeline problem -- the recent slowdown, instead of the expected acceleration, in innovative medical therapies reaching patients, and suggestions for addressing this problem.

Today's revolution in biomedical science has raised new hope for the prevention, treatment, and cure of serious illnesses. However, there is growing concern that many of the new basic science discoveries made in recent years may not quickly yield more effective, affordable, and safe medical products for patients. This is because the current medical product development path is becoming increasingly challenging, inefficient, and costly. During the last several years, the number of new drug and biologic applications submitted to FDA has declined significantly; the number of innovative medical device applications has also decreased. In contrast, the costs of product development have soared over the last decade.

Because of rising costs, innovators often concentrate their efforts on products with potentially high market return. Emerging contenders for resources include the development of products targeted for important public health needs (e.g., counter terrorism), less common diseases, prevalent third world diseases, prevention indications, or individualized therapy is becoming increasingly challenging. In fact, with rising health care costs, there is now concern about how the nation can continue to pay even for existing therapies. If the costs and difficulties of medical product development continue to grow, innovation will continue to stagnate or decline, and the biomedical revolution may not deliver on its promise of better health.

The problem, in FDA's view, is that the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process. For medical technology, performance is measured in terms of product safety and effectiveness. Not enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs. In many cases, developers have no choice but to use the tools and concepts of the last century to assess this century's treatment candidates. As a result, the vast majority of investigational products that enter clinical trials fail. Often, product development programs must be abandoned after extensive investment of time and resources. This high failure rate drives up costs, and developers are forced to use the profits from a decreasing number of successful products to subsidize a growing number of expensive

failures. Finally, the path to market, even for successful candidates, is long, costly, and inefficient, due in large part to the current reliance on suboptimal assessment methods.

A new product development toolkit -- containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques -- is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product. Superior product development science is needed to address these challenges -- to ensure that basic discoveries turn into new and better medical treatments. More efforts need to be directed at creating better tools for developing medical technologies. And we need a knowledge base built not just on ideas from biomedical research, but also on reliable insights into the pathway to patients.

FDA is planning an initiative that will identify and prioritize (1) the most pressing development problems and (2) the areas that provide the greatest opportunities for rapid improvement and public health benefits. This will be done for all three dimensions along the critical path -- safety assessment, evaluation of medical utility, and product industrialization. It is critical that we enlist all relevant stakeholders in this effort. We will work together to identify the most important challenges by creating a Critical Path Opportunity List. Concurrently, FDA will refocus its internal efforts to ensure that we are working on the most important problems and intensify our support of key projects.

Through scientific research focused on these challenges, we can improve the process for getting new and better treatments to patients. Directing research not only to new medical breakthroughs, but also to breakthrough tools for developing new treatments, is an essential step in providing patients with more timely, affordable, and predictable access to new therapies. We are confident that, with effective collaboration between government, academia, and the private sector, these goals can be achieved.

Conclusion

FDA is working with NCI, industry, academia, patient and other organizations to ensure that cancer patients receive safe and effective drugs. FDA is also working hard to improve patient access to promising cancer treatments without compromising patient safety. Furthermore, we are working to ensure that patients have timely and important information about available cancer drugs. Our goal is to improve upon a system that supports cancer patients, and all other patients seeking access to new drugs and treatments for their disease.

Thank you for the opportunity to testify. I will be happy to answer any questions the Committee might have.

Chairman TOM DAVIS. Thank you both. Let me start. We'll take 5 minutes.

Dr. Christian, the witnesses on our second panel today are going to cite lack of physician education as a barrier to adequate accrual in clinical trials. You talked briefly, but I wonder if you could elaborate on what efforts the National Cancer Institute has taken to inform physicians about the cancer trial support unit program. I mean, it seems to me that's where the word needs to get out. People go see their doctor, they get the diagnosis, they want a list of options. I think you'd just be teaming with people who want to get in on the latest and be a part of this, but it really starts and ends with the physician that they're treating who really gives them their menu of options.

Dr. CHRISTIAN. Well, I think that is absolutely correct. The NCI and the Cancer Trial Support Unit have worked with a number of organizations, the Coalition for Cooperative Groups being one, since they are intimately involved in that, but also with the American Society for Clinical Oncology and others, to make physicians aware of the opportunities to participate in trials through the Cancer Trials Support Unit. They also use electronic systems——

Chairman TOM DAVIS. Let me ask this. In continuing medical education, do you have requirements of that? I don't know if you have it in every State, but in most States is this part of it?

Dr. CHRISTIAN. To my knowledge it is not part of continuing medical education requirements. We do offer sessions, however, at national meetings so that there are educational opportunities there, but it is not a requirement, per se.

Chairman TOM DAVIS. I mean, it just seems to me when you're going in every year to get updated, that menu option, it's pretty easy to include it. If I were a physician, I'd sure want to know it and be able to give my patients that option, particularly some of those that don't have a lot of good options, as you're working on.

Dr. CHRISTIAN. Can I just elaborate also?

Chairman TOM DAVIS. Yes, please.

Dr. CHRISTIAN. We have also, working with the Cooperative Groups and others, invested quite heavily in patient education, because having patients be aware of clinical trials and requesting those opportunities of their physicians, I think is another way to approach this problem, and so we have, I think, all made major efforts to improve the education of patients about these opportunities.

Chairman TOM DAVIS. I think you touched briefly, but Dr. Comis of our next panel is going to testify that the National Cancer Institute only reimburses physicians about $2,000 per case to perform research in community-based physician practices, while studies suggest the cost is closer to $4,000. Is it possible, working with NCI's budget, to increase the allocation to offset these costs? Physician reimbursements are low on everything. This is an area where you really don't want to do it on the cheap.

Dr. CHRISTIAN. Well, the cost at a site for conducting clinical trials has been a subject of great interest and concern to us. During the 5-year period that I showed on my slide, there was a 62 percent increase in funding to the group system overall. But importantly, I think, funding to the sites actually doubled during that period.

So while $2,000 remains perhaps meager, it represented a substantial increase in what we had been able to fund previously. So we are continuing to seek ways to increase funding and to think about how best to allocate the clinical trials resources that we have overall so that we get the work done.

There are a number of groups—Dr. Comis and I work on several of them—that are actually trying to nail down much more precisely what the real components of cost are so that we can make, I think, more effective judgments in terms of how we are able to fund.

Chairman TOM DAVIS. I don't mean to single you out. Our reimbursements that we allocate to physicians under Medicare and Medicaid are pitiful, so I hear you.

Dr. Pazdur.

Dr. PAZDUR. I just wanted to jump in. Having done clinical trials for almost 20 years, there is a difference between knowing if they exist and actually doing them. OK? And I think people have to understand that the enrollment of a patient when one is conducting a busy practice is a very time consuming activity. It requires infrastructure to be present. It requires data managers. It requires research nurses. So there has to be an infrastructure within a clinician's practice that will allow him to do the clinical trials that he views to be of importance.

It is an issue, and I think when we take a look at the whole issue of why patients do not participate in clinical trials, to leave out the physician component is one that would not be appropriate. It is, as you pointed out, the physician that ultimately will be prescribing the therapy that the patient will be getting, and he has to have the appropriate incentives and also the infrastructure that will allow him to place patients on trial.

Chairman TOM DAVIS. Let me ask you, just so I know, understand, how many investigational products fail in clinical trials? I mean, the ratio compared to products approved, any idea? Ball park?

Dr. PAZDUR. I could—the vast majority of them. It's a small—probably our critical pathway states that one—if you take five drugs that are being developed in their very earliest stages, probably one will make it to the market.

Chairman TOM DAVIS. OK. Thank you very much.

Mr. Waxman.

Mr. WAXMAN. Dr. Christian, the Clinical Trials Cooperative Groups Program at NCI, they play a key role in clinical research against cancer. I know you're familiar with that. Studies by these networks of researchers have led to major advances in survival, particularly in the pediatric cancers, but we have a chart showing that the funding for this program has not increased in the last several years. And Dr. Comis, who is chair of the Coalition of National Cancer Cooperative Groups is going to testify that current funding stifles innovation, destabilizes key functions such as our tissue banks, data management, and informatics platforms, and acts as a disincentive to both academic and community physician participation. You can see from that chart there is a decrease for leukemia, gynecologic oncology, breast, and bowel cancer. How do you respond to the view that this important research program is threatened?

Dr. CHRISTIAN. Well, I can't see the details there, but my slide also covered, I think, some of those years, and, as I point out, we actually substantially increased funding over a significant portion of that time. Now, with that said, I think that there is no doubt that the costs for enrolling a patient at a site still are not being reimbursed at the proper rate. I think that is something that we continue to need to address.

You know, I think that there are many components of the clinical trials program. There is the Cooperative Groups Program, which is extremely important, as you point out, but there are many other critical elements, too, and I think that, given all of the new targeted agents that are coming into the clinic, the early clinical trials are extremely important, too, in advancing regimens to the point that they can go to phase three trials, and, indeed, many of those have been funded at much higher rates and, in fact, new resources have been created to try to get those new novel agents into a point where they can go to phase three trials, so——

Mr. WAXMAN. Do you agree that with less money and rising expenses the Cooperative Groups will have a harder time recruiting patients and doctors to their clinical trials?

Dr. CHRISTIAN. I think that with less money at each site that would be true, and our approach to that actually is to look at the entire clinical trials program and find ways to better integrate, to make the cost of putting patients on clinical trials lower by having consistent and standard approaches to data collection and other things that cost time and money. Data managers, as Dr. Pazdur pointed out, are one important component.

So we are trying to look across the system and find places where we can better integrate, conserve resources, and then allocate them to the places that need them the most so that we can, indeed, raise the funding at the sites where the research is actually being done.

Mr. WAXMAN. Given the NCI's emphasis on the genetics of cancer and the importance of tissue banks, what is NCI doing to enhance the role of the tissue banks run by the Cooperative Groups?

Dr. CHRISTIAN. Well, NCI actually has put forward a request recently for proposals for funding for tissue banks. We are planning not only to increase the funding for tissue banks because we agree that it is a really critical component of this research, but to actually stabilize that funding by awarding grants specifically to that purpose. So, rather than just general Cooperative Groups funding, we are going to provide additional funds specifically targeted to tumor banks in our Cooperative Groups.

Mr. WAXMAN. As NCI reorganizes itself to deal with the challenges of the future, I think it is important not to undermine those resources such as the Cooperative Groups that are the bedrock of our clinical research efforts, and I'm sure you agree with that, as well.

Dr. CHRISTIAN. I agree absolutely.

Mr. WAXMAN. Dr. Pazdur, clinical trials are a key tool in our fight against cancer, but they also can provide one of the few sources of hope for those people who have failed standard treatment options. The Web site, www.clinicaltrials.gov, is a searchable, online registry of clinical trials that patients with serious or life-threatening disease and illness and their providers can use to see

if they are eligible for participation. I'm sure you're familiar with this Web site.

Now, Federal law requires that the sponsor of any effectiveness study conducted under an investigational new drug proposal register with the data base within 21 days of the start of the patient enrollment. In April 2003, FDA reported that many sponsors of clinical studies of cancer treatments had not submitted the information to the registry. While 91 percent of NIH- and NCI-sponsored studies had been posted, only 47 percent of industry-sponsored studies had been posted, even though FDA had released a detailed guidance for industry in March 2002. Do you think increased industry compliance would benefit patients?

Dr. PAZDUR. The answer to your question is emphatically yes. We also are greatly concerned about the low participation of industry in listing their trials on www.cancertrials.gov. We have taken a concerted effort to try to find why, what is the reason, and I really don't have a good reason at that time if I could say, you know, this is the reason why industry is not placing studies on the Web site. One would think they would have every reason to place their trials on. If we're talking about poor accrual to clinical trials, industry can't cry about poor accruals to clinical trials if they are not putting it on the Web site.

In our own division and at the FDA, in general, after every phase two meeting and industry meeting we have a written bullet that is part of the minutes to that meeting that specifically informs the sponsor of the existence and their obligation to list the Web site. That is a written part of the minutes of every end of phase two meeting.

We've taken concerted efforts to talk to patient groups, to encourage patient advocates to advocate for participation of commercial sponsors to list their trials. In addition to that, we've taken a concerted effort of talking to industry about this.

There may be some concerns of confidentiality in listing clinical trials on www.clinicaltrials.com. I really don't buy that, Mr. Waxman.

Mr. WAXMAN. Well, I'm disappointed we couldn't get a PHRMA representative come in and testify today. It's ironic that, while they're refusing to comply fully with the Government Web site, PHRMA has a Web site, and on that PHRMA Web site there are—it's called, "New medicines and development," and on the PHRMA Web site they'll often list clinical trials that they're not listing on the Government Web site, but on their Web site they frequently don't include eligibility details on clinical trials or provide contact information for the trials. I don't know why companies may list information about studies in a form that's not useful to the patients, because if you read about it, you want to find out more about it, there's no contact information.

What is FDA going to do to enforce participation in the Web site?

Dr. PAZDUR. At this point we obviously have a process where we are communicating with the sponsors. We are trying to find out reasons why they are not putting the trials on this. We have begun an education program, as I pointed out, where at every meeting we are asking them and informing them of their obligation to do so.

In addition to that, we have a massive process during professional education to encourage physicians and to encourage patients to utilize this resource. We are somewhat limited on what we can do. We can educate, we can talk.

Mr. WAXMAN. Well, thank you very much.

Chairman TOM DAVIS. Thank you very much, Mr. Waxman.

Judge Carter.

Mr. CARTER. Thank you, Mr. Chairman.

Richard Nixon was President of the United States in 1970 and he declared war on cancer. He said our goal was to cure cancer in our lifetime. Well, he's dead. We haven't even come close. We spent $52.5 billion under the theory the Government could come up with a solution, and it is my understanding—and please correct me if I am wrong—that if you view the overall war on cancer, it has been a pretty bad failure. If you compare it to other wars in health areas, like heart disease, for instance, there has been much more success. Are we doing something wrong in our direction on the war on cancer as you see it? That's the question that's really concerning me, because where I come from there's a lot of folks dying of cancer. They don't see a whole lot of hope and they don't see a whole lot of success.

Do either one of you want to comment on why this—$52 billion and 35 years—hasn't succeeded in any way?

Dr. PAZDUR. I hear you. OK. I sympathize wholeheartedly, having had patients and family members with this disease. I think it is important for us to understand that cancer is not one disease. As Michaele pointed out, at this time we can say it is 100 diseases, but probably it is even many more diseases on a molecular basis.

The riddle of cancer I feel is far, far more complicated than, for example, the problems that we face with HIV infections where we know the ideology, we know the virus that is causing the problems. For most cancers we have very limited or rudimentary knowledge of what causes the cancer, and even sometimes the natural history and the variations.

For example, even what we call breast cancer probably is hundreds and hundreds of different diseases. The problem is the science. We have to make scientific advances, and that is on the basic level. We are beginning to do so, I feel, by understanding the genetic causes of cancer. We have seen some drugs that have dramatically changed the face of some diseases. While you are entirely right, if you took at look at the entire scope of cancer, one would have to look at it somewhat pessimistically. However, there are some diseases—for example, CML, a disease that when I began my medical career that was uniformly fatal with drugs that we used from the 1950's to treat it, which now we have a drug called Glevic, which transformed that disease into probably a chronic disease. One can't use the word "cure" at this time with many of these diseases, but clearly was an important medical development.

Why did we develop this drug? What gave us the capabilities? It was the basic understanding of the genetics of the disease, the molecular pathogenesis of the disease, and marrying that basic understanding of the disease with a therapy that interacted here. I think that is going to be the overriding principle as we take a look at newer drugs, understanding the disease on a molecular basis and

then drugs that are targeted toward molecular abnormalities or molecular deficiencies.

This is an area that I think is evolving, and I am somewhat pessimistic with the past, but on the future I am very optimistic that we are exactly—or we are now beginning to have the tools that will enable us to move forward.

Mr. CARTER. About 3 weeks ago Lance Armstrong has a cancer survivor group in Austin, TX, and I went to that, and it was very uplifting about all these cancer survivors, but when you cut through it the definition of a cancer survivor is they survived the first round, really. There's an awful lot of people there that, although they are in remission right now, they face the distinct possibility of seeing the cancer again, and it ultimately killing them. Where I stand from, cure of cancer means you go in, you get treated, and you're not going to have cancer, that cancer at least, again.

So we haven't reached that point, I understand, on almost anything but maybe childhood leukemia maybe where we've got a handle on it to some extent, so I'm just concerned about that much money and that much time and that little success, and I'm wondering, is there something innovative we can look at that would stimulate the challenge of the market go to out to win cancer? I firmly believe that if I could invent something to cure cancer I could be, you know, richer than Microsoft, and I think we ought to be able—somebody ought to be able to come up with some incentive to do that.

A question I want to raise—and I realize my time is gone, Mr. Chairman, a few more minutes—the question I want to raise is the issue on the development of drugs. Is that becoming a stumbling block to giving incentive to private enterprise to take on full-fledged the challenge of cancer treatment. It takes you 9 or 10 years to approve a cancer drug, gives you another 9 years to recover your cost if you're in the business of inventing or creating that cancer drug. Could we change our intellectual property laws to give a longer time after approval where you still have the assurance of a trademark, a patent which might enhance the ability of private industry to invest the kind of money they are going to invest to go into fighting cancer? How do you feel about that?

Dr. CHRISTIAN. I'd like to comment on that, and then I'd like to comment also on your previous question.

You know, I think that intellectual property issues are certainly a problem, particularly for combination treatments, particularly when we want to look at a much broader range of cancers than the more narrowly focused FDA approval pathway, for example. And, you know, I think it is possible that incentives might encourage industry to work more broadly with NCI, with each other, etc., so that we can do the combinations and do the broader development that will speed up this whole process, so I think that there are issues there that are probably worth looking at.

I mean, we, for example, have been following the Best PHRMAceuticals for Children Act to see what the impact of that might be on drug development, and I think that will give us some notion, so I think intellectual property is probably an issue that warrants further thought.

With regard to where we are with cancer, though, you know, I do want to point out that there are, you know, a growing list of tumors where we actually do cure patients and do prolong survival by adding treatment to surgery. You know, I think 20 years ago the list was negligible and now there is a growing list of situations where we actually do cure patients, and many more where we prolong their lives. So your pessimism I understand, but we have made progress, and I think, like Rick, that, given the array of new entities that we have to use and to develop at this moment, molecularly targeted entities, I am more optimistic than I have been in 20 years of therapeutics development that we actually may make fundamental molecular strides.

Of course, the case that he gave with Glevic and chronic myelogenous leukemia is one example. The reason that the numbers remain so daunting is that the major solid tumors—lung cancer, colon cancer—are much more complex molecularly, and so we are going to take a little bit longer, I think, to sort out what the relevant targets there are.

But it is very interesting—in two major medical journals this past month, "The New England Journal of Medicine" and "Science," there were articles about a mutation found in patients with lung cancer which may help explain how we should better use some of these new targeted agents that we are investigating. It was the first such article, so we are really very optimistic, again, that we are entering a period where we really are going to understand the molecular nature of these tumors and how to treat them.

Chairman TOM DAVIS. Thank you very much.

Mr. CARTER. Thank you, Mr. Chairman.

Chairman TOM DAVIS. Yes, sir, Mr. Murphy.

Mr. MURPHY. Thank you, Mr. Chairman. I have a lot of questions. Let's see what I can get through here.

First of all, there has been some frustration in the Hillman Cancer Center in Pittsburgh trying to recruit minority members for these studies—these are more than just racial minorities. These are also socioeconomic minorities—getting them to sites. Statistically speaking, do you believe there are significantly fewer minorities in studies on cancer trials nationwide? Is that a concern? Are there other things we need to be doing to recruit people of various income levels, a wide range of income levels, etc.?

Dr. CHRISTIAN. There are some situations with NCI-sponsored clinical trials where minorities are not accrued in proportion to the numbers that one would expect based on the prevalence of the cancer, for example. That's particularly true of African American men. It's true of Asian men and women. It's true of Hispanic men and women. And there are a lot of efforts ongoing, both in NCI-sponsored trials and at the cancer centers, University of Pittsburgh being one that has a funded grant actually to look at what some of the barriers are to accrual for racial and ethnic minorities and for people of lower socioeconomic status and for the elderly, which are also under-represented on clinical trials. So this is an issue that is important to us, and we are approaching it from a variety of different perspectives.

In our cancer centers I think, for reasons that are not altogether clear to me, there are some even greater disparities, so they have

an even harder time than we do to our national trials accruing what would seem to be a representative and reasonable number of minorities.

I chair actually the Task Force for the American Society of Clinical Oncology on Health Disparities and Workforce Diversity, and there are many issues that have to do with trust in communities, which have to do with the very, very low representation of minority medical professionals who might be able to reach these communities in more effective ways, so there are many issues. I think it is an important problem and one that we need to continue aggressively to try to address.

Mr. MURPHY. Let me move on to another area here that is important, and that has to do with the issue of people who may have insurance. Some States like California require insurance companies to cover clinical trials, and many other insurance companies will simply say they're not going to cover anything experimental. I'm not sure whether other States in addition to California have these laws. My question is this: has there been a cost/benefit analysis on these things, because there are times when people feel they are desperate and they want to try anything and the insurance company may say, "No, we're not going to cover that. There's simply no efficacy to support this and it appears to be very expensive." Have we done any sort of analysis overall? Is that ongoing?

Dr. CHRISTIAN. There have been a couple of studies looking at the incremental cost of care on clinical trials which have shown that they are not significantly higher than care delivered outside of clinical trials.

Mr. MURPHY. What does "significantly higher" mean?

Dr. CHRISTIAN. I don't remember what the actual dollar amounts were. Do you remember that?

Mr. MURPHY. Rough idea? Percentage?

Dr. CHRISTIAN. Yes, I can certainly provide those precise details, but the estimate is around 5 percent.

We have attempted to look at those incremental costs, but I think in addition there are other important things to consider here. Patients are going to be treated, and the treatments in the community may or may not be as well developed, as well based in evidence, and so there are costs associated with delivering——

Mr. MURPHY. Plus, you have differences in communities that may have a university medical center versus what might be in a community that might not be near some of those more advanced research.

Dr. CHRISTIAN. I mean, there are community participants in clinical trials, but there are also the vast majority of patients who are treated outside of clinical trials who are just treated in private practice settings. There, the evidence on which the treatments are based may or may not be as sound as that in the clinical trials. So I think there are a lot of things you have to take in account, but the cost concern, I think there is growing evidence that it should not be an impediment to providing those opportunities for patients through their health insurance coverage.

Mr. MURPHY. Thank you. That's all I have at this point. Thank you.

Chairman TOM DAVIS. Thank you.

Mr. Cummings.

Mr. CUMMINGS. Thank you very much, Mr. Chairman. I want to also thank you for holding this hearing. It is a subject I am very much interested in.

Dr. Christian, in my District I have Johns Hopkins, and I also have the University of Maryland Hospital, and one of the things that, in trying to get people involved in trials, not just for cancer, but trials, period, African Americans, is that there is a tremendous—and I think you mentioned it a moment ago in response to a question—a tremendous distrust. People cite the Tuskegee experiment. My mother, for example, says at one of those hospitals, if she is in dire straits on her death bed, don't stop there. And that's because they have seen and had rumors at least of African Americans who were experimented upon, and it causes them not to want—many people not to want to be a part of any kind of experiment. And so even when the argument is made that some of what they may have heard in the past isn't absolutely true, what seems to happen, just when we get to a point like, for example, with AIDS, for people to finally get right there at the doorstep to participate, something happens.

We have a situation we will be having a hearing here on the 18th where another hospital in my District tested some 2,500 patients and, come to find out, for AIDS and Hepatitis C, and come to find out the results, the machinery was malfunctioning. People knew it was malfunctioning and nobody did anything about it. So then when they hear that kind of information it makes it even worse, so they say, "Wait a minute. You're talking about AIDS and Hepatitis C, things that could be life threatening, and you mean to tell me I went to—" people have gone to the hospital, gotten results that may not be accurate, and nobody even waved a red flag.

So I was wondering, and I think that this is a situation that probably exists all over the country. And then, of course, with the whole issue of health care disparities, in the Congressional Black Caucus one of our No. 1 issues is health care disparities. African American people, as you well know, are dying early, suffering needlessly, and, as a matter of fact, just recently I was in an audience of about—I'd say about 400 African Americans in my District, and I asked how many of them believed in the last 5 years—within the last 5 years that they had a relative to die earlier than they should have because of some medical foul-up or to suffer serious injury because of something like that, and three-fifths of them raised their hand. I can cite situations in my own family, at least four or five, that I know things like that have happened.

So the question becomes: how do you deal with—how does—and we in the Congress, we not only have these hats that we wear here sitting on these panels, but we also take up the bully pulpit trying to get our constituents to do the right thing. Even when we pass legislation, we still want them to get out there and take the colon test and to do all those things to stay healthy. How do you say and how do you guarantee—not guarantee, but how do you assure people it's OK, particularly when they have these thoughts embedded in the DNA of every cell of their brain?

Dr. CHRISTIAN. Well, I appreciate the opportunity to talk about this a little bit. I grew up in a medical family and Tuskegee was

very real to us, too, and it was a real phenomenon. But I think that there have been many years since Tuskegee and there are many new protections for patients. I can assure you for NCI-sponsored trials, for example, that they are reviewed exhaustively by experts in the management of the cancer that we're talking about, by people at the National Cancer Institute, and by institutional review boards and others to ensure that the nature of the research is reasonable and ethical. That said, there clearly are health disparities across the entire spectrum of medical care.

I actually tell patients that on a clinical trial patients get the same treatment as everybody else. It is prescribed. It is written in a protocol. Exactly what needs to be done is written there and patients are treated according to that protocol. And we audit those sites. We go to the place and we look at the records and we make sure patients were treated the way they were supposed to be treated on the protocol, so there are even additional protections.

So there are many protections in place that I think make participation in an NCI-sponsored clinical trial a safe and reasonable thing. I think it is important for minority communities to benefit from the opportunity to participate and from the knowledge that is gained. There are concerns about whether there may be differences in the way various racial groups handle drugs, for example. We won't know that if we don't study them. We won't know that if we don't participate in trials. And so when the new drug is then approved for the treatment of some cancer, we won't know whether that actually benefits us as it does the rest of the population. I think it is important for us to be a part of that and to have the opportunity to have those treatments and to, you know, aggressively pursue those opportunities so that we are sure at least in that venue that we are getting comparable care.

So that's what I tell patients. I don't think patients should feel coerced to do it, but I think the opportunity should be made available to them.

Mr. CUMMINGS. Thank you.

Chairman TOM DAVIS. Thank you very much.

Let me just ask one final question, Dr. Pazdur. You raised concern in your testimony that the development of new cancer treatments will make clinical trials more costly and complicated. How do we address the concern if the criteria for enrollment in trials becomes based more on a patient's biological characteristics than clinical ones?

Dr. PAZDUR. Well, I think the eligibility criteria of the protocol will say patients must over express a particular enzyme, for example, and then patients will be enrolled that have that particular expression of the target that is aimed at. I look at this as a benefit to patients, to drug development, and to drug regulation because one of the problems obviously that we have in oncology today is even or most effective drugs are relatively modest in their response rate or in their clinical efficacy, so if we can predefine an enriched population that is more likely to benefit from the drug, that efficacy will be greater expressed, we'll have higher response rates, we'll have higher timed progression and better survival. Therefore, I look at it as a positive aspect for the whole area of drug develop-

ment, and I don't really look at it as an obstacle at all. I look at it as a positive thing.

Chairman TOM DAVIS. OK. Thank you both. Dr. Christian, thank you, as well. You have been very helpful, and I will allow you to go now and we'll go to our second panel. Thank you very much.

Before we do that, I want to welcome my colleague from New Jersey, Representative Scott Garrett, to our hearing. We'll take a 10-minute break because we just switched, and then, Dr. Garrett, I'll allow you to introduce one of our panel members.

[Break.]

Chairman TOM DAVIS. The committee will come back into order.

We are pleased to have our colleague from New Jersey here with us today. Mr. Garrett, you are recognized.

Mr. GARRETT. Thank you, Mr. Chairman. I appreciate the opportunity to introduce Dr. Andy Pecora, who is a 20-year veteran of the war on cancer. When I first met him, I knew a little bit about his background, now I know a whole lot more about his background and I would like to share that with the panel.

He is a graduate of Seton Hall back in 1979. He went on to receive his medical degree from the University of Medicine and Dentistry in New Jersey, the Great State of New Jersey, in 1983. He completed his residency over at New York Hospital, Cornell Hospital Systems, and then moved on to the Memorial Sloan Kettering Cancer Center and completed a fellowship in hematology and oncology in 1989, after which he moved on to Hackensack University Medical Center to serve as director of hematology and oncology in the adult blood and marrow transplant program, and now has recently been promoted to chairman and director of the Cancer Center at Hackensack University Medical Center.

He is a diplomat of the American Board of Internal Medicine with subspecialties in hematology and subspecialties in oncology, and he has received numerous awards and honors, some of which include the Women's Guild Premedical Academic Achievement Scholarship back in 1978. In 1979 the Academic Excellence Award in Biology. In 1983 the Doctors Milton and Rose Petrokowski Award for Overall Excellence in Patient Care. And then the Outstanding Teacher Award from the Department of Internal Medicine at Hackensack University Medical Center in 1989. And for all doctors I think this is important—he was selected as one of the best doctors in America in 1997, 1998, and 2003, and then received the American Cancer Society Physicians in the Forefront Award and the Susan G. Komen Breast Cancer Foundation Award as a hero in the fight against breast cancer. He received the EBMTESMO Award at the International Conference on High Dose Chemotherapy in Breast and Ovarian Cancer.

His professional positions include such things as the scientific advisor for the companies ProNeuron and ProVirus. In addition, he has co-founded and served as chairman and chief executive officer of Progenitor Cell Therapy and now serves on the Board of Directors of the American Society of Bone Marrow Transplant, and previously on the International Society of Hemotherapy and Graft Engineering, the Hackensack University Medical Center IPA, and served as chairman of the medical board and board members of the Affiliated Physician Network.

In addition to these things, he has served as chairman of the Transplantation Committee on the International Society of Hemotherapy and Graft Engineering and served as a member of the Cancer Institute of New Jersey Protocol Advisory Committee.

Recently, he was appointed to the Steering Committee on the Transplant Treatment Trials Group, and he is a fellow of the Academic Academy of Medicine of New Jersey and a fellow of the American College of Physicians and American Society of Clinical Oncology and American Society of Oncology.

Finally, the doctor has been involved in numerous research projects in an effort to improve the outcome of patients with cancer. His recent work includes the production of stem cell products that are free of contaminating malignant cells using technology including CD–34 selection and ex vivo expansion. He has led several national trials in the field of transplantation and has published numerous peer reviewed articles and abstracts and has presented the results of his research at many national and international scientific meetings.

Probably most importantly, he is married and has three great children and resides in the fair State of New Jersey in the beautiful town of Ridgewood.

We welcome you to the panel.

Chairman TOM DAVIS. Thank you very much, Dr. Pecora. Thank you very much. We are joined here today with Dr. Robert Comis, who is president of the Coalition of National Cancer Cooperative Groups and is a professor of medicine and director at the MCP Honoman University Clinical Trials Research Center in Philadelphia; and Ms. Ellen Stovall, who is a 28-year survivor of two bouts with cancer and president and CEO of the National Coalition for Cancer Survivorship.

This panel of witnesses is going to provide the committee with their perspective on the seriousness of low accrual levels in cancer clinical trials and what efforts are being taken to improve outcomes in cancer patients. They are obviously a very distinguished panel. We appreciate all of you being with us.

It is our policy to swear everyone in, so if you would rise with me and raise your right hands.

[Witnesses sworn.]

Chairman TOM DAVIS. Thank you.

What we will do is your entire statement is already part of the record. Dr. Pecora, I'll start with you. Try to do it within 5 minutes. You have your lights there that turn orange after 4 minutes, red after 5, and then we'll go straight down the line and then we'll move to questions. Thank you all very much for being with us.

STATEMENTS OF DR. ANDREW PECORA, CHAIRMAN AND DIRECTOR, THE CANCER CENTER, HACKENSACK UNIVERSITY MEDICAL CENTER; DR. ROBERT COMIS, PRESIDENT AND CHAIR, COALITION OF NATIONAL CANCER COOPERATIVE GROUPS; AND ELLEN STOVALL, PRESIDENT AND CHIEF EXECUTIVE OFFICER, NATIONAL COALITION FOR CANCER SURVIVORSHIP

Dr. PECORA. Thank you. Thank you, Mr. Garrett, for your kind words. First and foremost, thank you, Chairman Davis and distin-

guished committee members, for providing me the opportunity to participate in this important hearing that hopefully will result in actions leading to improve outcomes for people afflicted with cancer. I have been active in the war on cancer for over 20 years, participating in basic science, clinical trials, and now cancer care administration. I welcome the opportunity to share my ideas on why and how increasing participation in clinical trials, regardless of the status of innovation, will improve outcomes for people suffering with cancer.

We all well know that over the past 35 years Government, industry, and the public have spent billions of dollars to create and operate the agencies that oversee and fund efforts in basic and clinical discovery aimed to improve outcomes for people battling cancer. As a result, substantial advances have been made in the understanding of the biology of cancer and, as a consequence, new and more effective treatments have emerged.

Unfortunately, even with this focus and extensively funded effort, cancer remains a serious problem. This year in the United States, alone, cancer is expected to claim more than 500,000 lives; thus, criticism of our current system exists. In a recent article in "Fortune" magazine authored by Clifton Leaf, significant criticism is levied at the cancer research community claiming the culture is dysfunctional and that the search for knowledge has supplanted the search for cures, they lead to discoveries of marginal benefit regardless of a great expense of time and money. I believe, however, that these claims are only partially correct, and that, as a consequence of our national effort, it is now within our reach to turn cancer in most cases into a chronic disease much like diabetes, while searches for prevention and cures continue.

As Mr. Leaf eloquently points out in his article, we must make the entire system of discovery and application of new agents more efficient. Clearly, continued improvements in our understanding of the underlying root causes of cancer and methods of detection, of efficacy, and safety are essential. Of equal importance however is active and robust participation by people with cancer in clinical trials. No matter how promising a therapy appears in laboratory testing, it is only through clinical trials that safety and effectiveness can be established in people. Simply stated, no person or computer program is capable of predicting whether a new treatment will work and be safe in people. In my current experience, it is not the lack of good ideas that is slowing progress in our quest to cure cancer, but it is much more a result of the slow pace of completing active clinical trials.

In 2003, there were approximately 1,700 ongoing clinical trials, of which the NCI sponsored 1,200. Despite this large number of trials, only 3 percent of adult patients participated, while 20 percent were eligible. Low participation in clinical trials slows the continuum of drug development from initial concept to FDA approved products, and as a consequence impedes improvements of outcomes for people with cancer.

In addition, poor participation at clinical trials lengthens the new drug approval process, estimated now at 10 to 12 years, and has the cascade effect of increasing new drug development cost, now estimated at $800 million, inflating the cost of drugs to consumers

once approved, and, worst of all, limiting the number of new agents that make it through the process of the discovery pipeline.

Advances in knowledge which will lead to better questions should continue to be supported, but at the same time we need to improve participation in clinical trials. So what can we do about it? Lack of participation is due to several factors that can and should be addressed. A lack of public knowledge of availability of clinical trials and a growing public bias against participation due to poor outcome high profile cases is a key factor. Government should do everything it can to educate the public on the value and importance of participating in clinical trials.

In an era of shrinking reimbursement for clinical care, funding needs to be established for clinical programs, both hospital and office based, to support the required infrastructure, including research staff and informatics, to participate in clinical trials. Reductions in their growing regulatory burden, including centralization of institutional review boards, streamlining adverse event reporting, and minimizing regulation resulting in increased cost and complexity without compromising patient safety or privacy must also be accomplished.

Finally, insurance reimbursement for clinical trial cost needs to be addressed nationally. In my home State of New Jersey, I was a member of the New Jersey working group to improve outcomes in cancer patients. Our group was successful in convincing the insurance companies covering New Jersey residents to voluntarily reimburse for approved clinical trial related expenses. This could serve as a model for a national effort.

Another important aspect to improve outcomes for people with cancer is to have more clinical trials available. This can be accomplished by increasing the efficiency of moving clinical trial concepts through the approval process before they become available to the public. The current system should be more efficient and held to more businesslike timelines for results. Specifically, the Cooperative Groups in the national cancer review process takes too long, at times years, and should have efficiencies mandated by Government, since it is Government that supports these efforts. Moreover, encouraging and rewarding the national Cooperative Groups to work together on questions that require large number of patients to answer is essential.

Finally, the issues of creating an environment—intellectual property protection, FDA approval support, etc.—for multiple agents to be tested together for effectiveness prior to the FDA approval process needs to be addressed.

In summary, I believe this is an exciting time for those engaged in the battle against cancer. The fruits of our efforts over the past 35 years are just beginning to be realized. It is clearly no time to retreat or claim defeat, but instead refocus our energies to make the entire system more efficient, less expensive, and more user friendly. Our family and friends afflicted with cancer deserve our collective best effort. In doing so, participation in clinical trials should increase, resulting in meaningful answers and better answers sooner for those battling this dreaded disease.

Thank you. I am happy to answer any of your questions.

[The prepared statement of Dr. Pecora follows:]

TESTIMONY

Andrew L. Pecora, M.D. FACP
Chairman and Director
The Cancer Center at Hackensack University Medical Center
Clinical Professor of Medicine
University of Medicine and Dentistry of New Jersey

U.S. House of Representatives
Hearing before the Committee on Government Reform
"Harnessing Science: Advancing Care by Accelerating the Rate of Cancer Clinical Trial Participation"
May 13, 2004 10:00 a.m.
2154 Rayburn House Office Building

First and foremost thank you to Chairman Davis and distinguished Committee members for providing me the opportunity to participate in this important hearing that hopefully will result in actions leading to improved outcomes for people afflicted with cancer. I have been active in the "war" on cancer for over 20 years participating in basic science, clinical trials and cancer care administration. I welcome the opportunity to share my ideas on why and how increasing participation in clinical trials, regardless of the status of innovation, will improve outcomes for people suffering with cancer. Over the past 35 years, government, industry and the public have spent billions of dollars to create and operate the agencies that oversee and fund efforts in basic and clinical discovery aimed to improve outcomes for people battling cancer. As a result, substantial advances have been made in the understanding of the biology of cancer and as a consequence new and more effective treatments have emerged.

Unfortunately, even with this focused and extensively funded effort, cancer remains a serious problem. This year in the United States alone, cancer is expected to claim more than 500,000 lives. Thus, criticism of our current system exists. In a recent article (FORTUNE, March 22, 2004) authored by Clifton Leaf, significant criticism is levied at the cancer research community claiming the culture is "dysfunctional" and that the search for knowledge has supplanted the search for cures, leading to discoveries of marginal benefit regardless of a great expense of time and money. I believe, however, that these claims are only partially correct and that as a consequence of our national effort, it is now within our reach to turn cancer in most cases, into a chronic disease, much like diabetes, while searches for prevention and cures continue. As Mr. Leaf eloquently points out in his article, we must make the entire system of discovery and application of new agents more efficient. Clearly, continued improvements in our understanding of the underlying route causes of cancer and methods of detection of efficacy and safety are essential. Of equal importance, however, is active and robust participation by people with cancer in clinical trials.

No matter how promising a therapy appears in laboratory testing, it is only through a clinical trial that safety and effectiveness can be established in people. Simply stated, no person or computer program is capable of predicting whether a new treatment will work or be safe in people. In my current experience, it is not the lack of good ideas that is slowing progress in our quest to cure cancer, but it is much more a result of the slow pace of completing active clinical trials. In 2003 there were approximately 1700 ongoing clinical trials of which the NCI sponsored 1200. Despite this large number of trials, only 3% of adult patients participated while 20% were eligible. Low participation in clinical trials slows the continuum of drug development from initial concept to FDA-approved products and as a consequence,

impedes improvements of outcomes for people with cancer. In addition, poor participation in clinical trials lengthens the new drug approval process (estimated at 10-12 years) and has the cascade effect of increasing new drug development costs (estimated at $800 million), inflating the cost of the drug to consumers once approved, and worst of all, limiting the number of new agents that make it through the discovery pipeline. Advances in knowledge, which will lead to better questions, should continue to be supported but at the same time we need to improve participation in clinical trials.

Lack of participation is due to several factors that can and should be addressed. A lack of public knowledge of availability of clinical trials and a growing public bias against participation due to poor outcome high profile cases is a key factor. Government should do everything it can to educate the public on the value and importance of participating in clinical trials. In an era of shrinking reimbursement for clinical care, funding needs to be established for clinical programs (hospital and office-based) to support the required infrastructure (both research staff and informatics) to participate in clinical trials. Reductions in the growing regulatory burden including centralizing Institutional Review Boards (IRBs), streamlining adverse event reporting, and minimizing regulation resulting in increased cost and complexity, without compromising patient safety or privacy, must also be accomplished. Finally, insurance reimbursement for clinical trial cost needs to be addressed nationally. In my home state of New Jersey, I was a member of the N.J. working group to improve outcomes in cancer patients. Our group was successful in convincing the insurance companies covering N.J. residents to voluntarily reimburse for approved clinical trial related expenses. This could serve as a model for a national effort.

Another important aspect to improve outcomes for people with cancer is to have more clinical trials available. This can be accomplished by increasing the efficiency of moving clinical trial concepts through the approval process before they become available to the public. The current system should be more efficient and held to more business-like timelines for results. Specifically, the cooperative groups and the NCI review process take too long (at times years), and should have efficiencies mandated by government since it is government that supports their efforts. Moreover, encouraging and rewarding the national cooperative groups to work together on questions that require large numbers of patients to answer is essential. Finally, the issue of creating an environment (intellectual property protection, FDA approval support etc) for multiple agents to be tested together for effectiveness prior to FDA approval needs to be addressed.

In summary, I believe that it is an exciting time for those engaged in the battle against cancer. The fruits of our efforts over the past 35 years are just beginning to be realized. It is clearly no time to retreat or claim defeat but instead refocus our energies to make the entire system more efficient, less expensive and more user friendly. Our family and friends afflicted with cancer deserve our collective best effort. In doing so, participation in clinical trials should increase, resulting in meaningful answers and better outcomes sooner for those battling this dread disease. Thank you and I am happy to answer your questions.

Chairman TOM DAVIS. Thank you very much.

Dr. Comis.

Dr. COMIS. Congressmen Davis, Waxman, and members of the committee, I want to thank you for this opportunity to testify on behalf of 8,000 Cooperative Groups members from cancer centers, community practices, and patient advocacy groups across the country. Most importantly, we should all thank the courageous patients who enter our clinical trials. They are the real pioneers who move the frontiers of cancer treatment forward.

There are two distinct forces in cancer clinical trials—those studies directly supported by industry and overseen by the FDA, and those studies supported by the NCI which are conceived, designed, and executed in academic and community practices throughout the Nation. Typical industry supported trials are directed toward drug approval; Cooperative Groups trials are designed to evaluate new approaches and establish new evidence-based standards of care. We estimate that approximately 50,000 patients participate in clinical trials yearly. The NCI-funded Cooperative Groups account for about half, or 25,000 of those patients. The Cooperative Groups have always played a key role in the Nation's cancer research system. We develop curative therapies for childhood cancers, improve the post-surgical survival for patients with breast and colorectal cancer by 25 to 30 percent, and show that cancer can, indeed, be prevented in high-risk patients.

As importantly, though, the publicly funded system allows us to ask and answer questions that challenge the mainstream. Our studies evaluating high-dose chemotherapy for breast cancer showed that this extraordinarily expensive and toxic treatment was of no clear benefit, saving the country hundreds of millions of dollars and patients unquestionable toxicity.

Much has changed since President Nixon declared the war on cancer. The understanding of the biology of cancer has increased tremendously. The public and private sector has invested huge resources in the development of biologically directed therapies, and new targeted agents are entering the oncology practice in our phase two and three trials.

The Cooperative Groups have adjusted to the opportunities and challenges created by these changes. We are investigating the newest molecules and approaches. Virtually all of our studies now include laboratory correlative studies which attempted to find why something does or does not work. In order to do this, we've established excellent tissue banks and laboratory programs in cancer centers throughout the country which collect, store, and analyze tissue specimens and correlate biology with clinical events occurring in our controlled clinical trials. But we must do more to ensure that patients have the opportunity to benefit from our work.

First, let me address the issue of accrual of adults onto cancer clinical trials. We estimate that only about 3 to 5 percent of adult cancer patients participate in clinical trials. This number was confirmed prospectively in our survey, which we did along with Ellen's group, which also revealed that only 15 percent of patients were aware that participation was even an option. That survey also reinforced the critical role of the oncologist in informing and educating patients about this option. Increasing awareness, dispelling mis-

conceptions, engaging physicians are key elements of the solution to the accrual problem.

These considerations led the Coalition of National Cancer Cooperative Groups to launch a national awareness campaign along with "Newsweek," which is in its 4th year, develop Web-based tools to facilitate trial searches, and work with the American Society of Clinical Oncology in developing both recognition and educational programs for physicians.

Indeed, the efforts of the Coalition and others have born some fruit. There has been a 30 percent increase in overall accrual onto cooperative group studies from 1997 to 2002, from about 20,000 patients a year to about 26,000 patients, but more needs to be done. However, the system is stressed even at this level of accrual. The Cooperative Groups have been and remain chronically under-funded. Two extensive reviews of the system in the mid 1990's recommended that the Cooperative Groups be funded at the full peer recommended level. We continue to be funded at approximately 60 percent of that level, and funding has been flat for the last 3 years. This stifles innovation, destabilizes key functions such as our tissue banks, data management platforms, and acts as a disincentive to both academic and community physician participation.

Keep in mind that about 60 percent of accrual comes from community-based practices. The NCI reimburses $2,000 per case to perform the research at the site. It is estimated in the ASCO survey that the actual cost is more like $4,000 to $6,000 per case. The ability for both academic and community sites to continue in Government-sponsored work will be increasingly challenged, particularly when the full effect of the Medicare Modernization Act of 2003 takes place in 2005.

The entire system is being buried under a regulatory mountain. It is estimated that about 30 percent of clinical trials research dollars goes toward ensuring regulatory compliance.

Our studies are overseen by about 1,600 separate IRBs. HIPA compliance complicates our laboratory work. The current discussions about off-label drug use in oncology could have a huge impact on our studies, which try to explore new indications and uses for targeted agents as they become available.

We all believe that there is an important balance between the need for innovation and the critical societal concerns, but the balance must ultimately be struck for the advantage of all who suffer from cancer.

The Cooperative Groups remain totally committed to providing high-quality care and new opportunities for cancer patients, but rest assured the development of the newer cancer treatments will make clinical trials more complicated and more costly and accrual will remain a major concern.

The Cooperative Groups chairs have developed a white paper entitled, "Harnessing the Science: A Proposal to Improve the Publicly Funded Cancer Clinical Research System," which I have submitted

for the record, which outlines our thoughts on what can be done to ensure the continued vitality and importance of the Cooperative Groups in the publicly funded system, which is so critical to our cancer patients in the Nation.

Thank you.

[The prepared statement of Dr. Comis follows:]

"Harnessing Science: Advancing Care by Accelerating the Rate of Cancer Clinical Trials Participation"

House of Representatives Committee on Government Reform

Thursday, May 13, 2004

Rayburn House Office Building, Room 2154

Testimony of Dr. Robert L. Comis, M.D.

Professor of Medicine, Drexel University College of Medicine

Group Chair, Eastern Cooperative Oncology Group (ECOG)

President and Chairman, Coalition of National Cancer Cooperative Groups

Congressmen Davis, Waxman and members of the committee, I want to thank you for this opportunity to testify on behalf of the 8000 cooperative group members from cancer centers, community practices and patient advocacy groups across the country. Most importantly, we should all thank the courageous patients who enter our clinical trials; they are the real pioneers who move the frontiers of cancer treatment forward.

There are two distinct forces in cancer clinical trials: those studies directly supported by industry, and overseen by the FDA, and those studies supported by the NCI which are conceived, designed and executed in academic and community practices throughout the nation. Pivotal industry supported trials are directed towards drug approval. Cooperative group trials are designed to evaluate new approaches and establish new, evidence-based standards of care.

We estimate that approximately 50,000 patients participate in clinical trials yearly. The NCI funded cooperative groups account for about half, or 25,000 patients/year.

The cooperative groups have always played a key role in the nation's clinical research system. We developed curative therapies for childhood cancers; improved the post-surgical survival for patients with breast and colorectal cancer by 25-30%; and showed that cancer can indeed be prevented in high-risk patients.

As importantly, though, the publicly funded system allows us to ask and answer questions that challenge the mainstream. Our studies evaluating high dose chemotherapy for breast cancer showed that this extraordinarily expensive and toxic treatment was of no clear benefit—saving the country hundreds of millions of dollars and patients unquestionable toxicity.

Much has changed since President Nixon declared the War on Cancer. The understanding of the biology of cancer has increased tremendously; the public and private sector has invested huge resources into the development of biologically directed therapies, and new, targeted agents are entering the oncology practice, and our Phase II and III trials.

The cooperative groups have adjusted to the opportunities and challenges created by these changes. We are investigating the newest molecules and approaches. Virtually all of our studies now include laboratory correlative studies, which attempt to define why something does or does not work. In order to do this, we have established excellent tissue banks and laboratory programs in cancer centers throughout the country, which collect, store and analyze tissue specimens and correlate biology with clinical events occurring in our controlled clinical trials.

But we must do more to ensure that patients have the opportunity to benefit from our work.

First, let me address the issue of accrual of adults onto cancer clinical trials. We estimate that only bout 3-5% of adult cancer patients participate in clinical trials. This number was confirmed prospectively in our Harris Survey, which also revealed that only 15% of patients were aware that participation was an option. That survey also reinforced the critical role of the oncologist in informing and educating patients about this option. Increasing awareness, dispelling misconceptions and engaging physicians are key elements of the solution to the accrual problem. These considerations led the Coalition of National Cancer Cooperative Groups to launch a National Awareness Campaign along with Newsweek which is in its fourth year, develop web based tools to facilitate trial searches, and work with the American Society of Clinical Oncology in

developing both recognition and educational programs for physicians. . Indeed the efforts of the Coalition have borne some fruit. There has been a 30% increase in overall accrual onto cooperative group studies from 1997 to 2002- from about 20,000 patients/year to about 26,000. But more work needs to be done.

However, the system is stressed even at this level of accrual. The cooperative groups have been and remain chronically under funded. Two extensive reviews of the system in the mid 1990s recommended that the cooperative groups be funded at the full peer review recommended level. We continue to be funded at approximately 60% of that level, and funding has been flat for the last three years. This stifles innovation, destabilizes key functions such as our tissue banks, data management and informatics platforms, and acts as a disincentive to both academic and community physician participation.

Keep in mind that about 60% of accrual comes from community based physician practices. The NCI reimburses $2000/case to perform the research at the site. It is estimated in the ASCO survey that the actual cost is more like 4000-6000 dollars/ case. The ability for both academic and community sites to continue to do government sponsored work will be increasingly challenged, particularly when the full effect of the Medicare Modernization Act of 2003 takes place in 2005.

The entire system is being buried under a regulatory mountain. It is estimated that about 30% of the clinical trials research dollar now goes towards ensuring regulatory compliance. Our studies are overseen by about 1600 separate IRBs; HIPAA compliance complicates our scientific work. The current discussions about off label drug use in oncology could have a huge impact on our studies, which try to explore new indications, and uses for targeted agents as they become available. We all believe that there is an important balance

between the need for innovation and critical societal concerns—but the balance must ultimately be struck for the advantage of all who suffer from cancer.

The cooperative groups remain totally committed to providing high quality care and new opportunities for cancer patients. But rest assured, the development of the newer cancer treatments will make clinical trials more complicated and more costly. Accrual will remain a major issue as we enroll patients based more on their biologic characteristics than clinical ones.

The cooperative groups chairs have developed a White Paper entitled "Harnessing the Science: A proposal to improve the publicly-funded cancer clinical research system" which I have submitted for the record which outlines our thoughts on what can be done to ensure the continued vitality and importance of the cooperative groups in the publicly funded system which is so critical to cancer patients in our country.

Thank you,

Robert L. Comis, MD

HARNESSING THE SCIENCE – ADVANCING CARE:

A PROPOSAL TO IMPROVE THE PUBLICLY-FUNDED CANCER CLINICAL RESEARCH SYSTEM

Prepared by the Group Chairs of the Cooperative Groups working together
under the aegis of the Coalition of National Cancer Cooperative Groups

March 9, 2004

The Cooperative Groups have played a key role in the Nation's cancer clinical research system for almost half a century. The Groups, whose members include NCI-designated Cancer Centers, SPOREs, an extensive community-based provider network, and strong patient advocate programs have advanced the standards of care in cancer to save lives and to improve the quality of life of cancer patients. The Groups' pioneering work on adjuvant therapies, combined modality therapies, chemoprevention of cancer, and organ preservation has enabled countless cancer patients to become cancer survivors.

Although the Groups are recognized as the worldwide model for clinical research, the system faces numerous challenges that jeopardize its future. This proposal addresses the major challenges that hinder the cancer clinical research system and sets forth recommendations in five strategic areas:

1) Streamlining the clinical research structure and improving the working of its component parts;
2) Adapting the system to the development requirements of modern cancer therapies;
3) Establishing scientific priorities;
4) Accelerating protocol development; and,
5) Improving funding.

The Group Chairs would like to express their gratitude to the Coalition's Patient Advisory Board for their support in the development of this proposal. They are confident that by implementing the recommendations outlined in this proposal the system will become more responsive to the needs of investigators and the patients they serve. The Group Chairs look forward to collaborating with the NCI Director in a concerted effort to improve the national cancer clinical research system.

Mission and Background

The Mission of the Cooperative Groups is to save the lives of cancer patients and advance the standards of care for cancer patients through publicly-supported clinical trials and correlative studies that are definitive, controlled, investigator-initiated, multi-center, and peer-reviewed. As the only public alternative to industry, Cooperative Groups optimize the discovery, development, and delivery of new cancer screening, diagnostic, and therapeutic approaches, as the results of their studies are integrated into standard practice. The Groups and their affiliated community members conduct definitive multi-center Phase III trials that assess novel therapeutic interventions and validate surrogate end points and hypotheses that are generated by the academic oncology community, including Cancer Centers and SPOREs, all of which are affiliated or participate with the Cooperative Groups.

Throughout their history, the Groups have been an indispensable resource in the discovery, development, and delivery continuum that produces new cancer treatment and prevention strategies. By involving community doctors in their trials, the Groups have become the engine for advancing the standards of care in a real-world setting, establishing what should be delivered. Their track record in reducing the burden of cancer is unmatched.

Major clinical accomplishments include:

- Demonstrating the benefits of adjuvant therapy in colon, lung, prostate, breast, ovarian, and cervical cancer;
- Developing combined modality therapies for solid tumors;
- Substantiating the use of chemoprevention in cancer; and,
- Developing curative therapies and dramatically increasing long-term survival rates in childhood and adolescent cancer patients.

For example, the National Surgical Adjuvant Breast and Bowel Project's (NSABP) Breast Cancer Prevention Trial (BCPT/P-1) results established the proof of principle that the incidence of breast cancer can be reduced, which led the FDA to approve the use of tamoxifen to reduce the risk of breast cancer in women at increased risk for the disease, the first such approval. Since the BCPT results were first reported, other large cancer prevention trials have shown positive results in breast, colon, and prostate cancer (for example, the prostate cancer prevention trial comparing finasteride with placebo). Additional prevention and early detection trials have been initiated and are well underway, setting the stage for further advances, much like the process that occurred 25 years ago with the first adjuvant therapy trials in breast cancer.

The vast majority of Group trials include correlative studies performed in laboratories throughout the country. The Groups' high-quality laboratory studies have yielded a rich harvest of important results. Some examples include demonstrating the relationship between Her-2/neu expression and anthracycline responsiveness in breast cancer, confirming 18q/MSI as a marker of colon cancer prognosis, developing risk-adapted therapies for leukemia, and showing the predictive value of EGFR overexpression in head and neck cancer patients.

The NCI clinical trials structure epitomizes the types of integrated research teams recommended in the NIH Roadmap initiative, and should be the model for future efforts. The Groups manage more than 100,000 patients annually on high-quality clinical trials – therapeutic, prevention, translational, symptom-control, early-detection, and diagnostic. Of those 100,000 patients, approximately 25,000 are enrolled annually on therapeutic trials, representing one half of all patients on therapeutic trials in the country. The Groups provide access to broad patient populations for large-scale randomized trials, and have spearheaded minority-access, community-based programs, and studies of special populations. The Groups have also woven patient advocate participation into their organizations on a national scale, providing them with a unique platform to optimize the design of clinical trials and a voice to recommend improvements to the clinical research system.

Despite its singular role and contributions, the system faces chronic and harmful issues that threaten its ability to fulfill its Mission. The Armitage Committee and Implementation Committee Reports acknowledged many such issues during the late-1990s. In September 2002, the NCI Director's Consumer Liaison Group (DCLG) and the Coalition's Patient Advisory Board (PAB) produced a report evaluating the pilot programs that were created as a result of the Armitage Committee Report and the recommendations of the Implementation Committee. A major conclusion of the DCLG/PAB report is that the challenges plaguing the system persist, and, in some cases, have worsened. For example, activating a trial has become a longer and more complex process, with additional review layers. Funding levels continue flat and remain insufficient to cover costs. The autonomy of individual investigators, the driving force for innovation in the Groups, appears constrained as the scientific agenda is controlled, rather than facilitated, by NCI. And, core laboratories and informatics enhancements continue to be inadequately resourced.

One result is that the system's most important professional constituency, clinical researchers, is questioning the value of continuing to participate in Group studies. For current and future patients, the lengthy time to trial activation means that many will not receive treatment that could represent their best hope for survival.

Recommendations

The Group Chairs are committed to invigorating the system, making it more attractive to researchers and more vital as a force in helping to advance the standards of care in cancer. In their deliberations during the past year, the Group Chairs have developed recommendations that they believe will animate the system and give it renewed vigor to achieve its Mission. The remainder of this proposal articulates these recommendations, and classifies them by the five strategic goals listed in the introduction.

The Group Chairs are confident that, with the support of the NCI to help implement the recommendations, the time to trial activation will be significantly reduced and that the number of completed, high-quality trials will increase. In the process, the value of the system to patients and investigators will continue to grow as the important hypotheses in cancer prevention, early detection, and treatment are validated.

1. Streamlining the Clinical Research Structure

The Cooperative Groups, which include NCI-designated Cancer Centers, SPOREs, CCOPs, and other academically affiliated practices are an integral part of the Nation's cancer clinical research system. Every Cancer Center is a participant in at least one Cooperative Group, and Cooperative Groups serve as research bases for the CCOPs. Cancer Centers holding SPOREs are also members of the Cooperative Groups. In all, more than 1,500 institutions throughout the United States and Canada, and approximately 8,000 investigators in these institutions participate in Cooperative Group trials. The components complement each other: As Centers and SPOREs drive the early stages of the discovery and development processes, the Groups and CCOPs primarily fulfill the latter stages of the development and beginning stages of the delivery end of the process.

Unfortunately, the components of the system tend to function as a collection of disparate programs, as opposed to one integrated public system. The Group Chairs believe that the guidelines governing the Centers, SPOREs, and Groups should be harmonized to engender more cooperation and data-sharing (including, tissue and images) among the major programs. For example, because standards of care cannot be advanced without Phase III trials, the Group Chairs recommend that the performance of SPOREs and Centers should be measured, in part, by the number of agents, ideas, or approaches that move into Phase II and Phase III Cooperative Group trials. Similarly, the peer-review criteria should be modified to eliminate disincentives to cooperation and to encourage and reward collaboration. Financially, Centers and SPOREs should receive incremental funding if they participate in Group trials, for instance, when they serve as reference laboratories or provide bioinformatics expertise. There should be no unfunded mandates or disincentives to achieve participation across the entire system. Patient advocates, who are involved in the review of each program's guidelines, should be included in the harmonization effort.

Another powerful way to improve collaboration is to eliminate restrictions on the mobility of investigators. Today, the unit of membership in most of the adult Groups is the institution, not the individual. Consequently, investigators are tied to their institutions, which means that the system cannot readily access the best minds for science and leadership positions. The Group Chairs propose to remove the barriers to improving the system, in part, by providing investigators access to the system's facilities, regardless of institutional affiliation.

The existence of separate Groups enriches the scientific platform, because it permits each Group to develop areas of special expertise. At the same time, a decentralized structure can lead to replication of functions such as administration and operations across the system. A starting point in generating cross-Group efficiencies would be to explore the consolidation or centralization of some of these functions. Before embarking on such a course, however, the Group Chairs recommend that the lessons of the merger of the pediatric groups into the Children's Oncology Group (COG) be fully evaluated. Although the merger has been successful, it was more difficult and time-consuming than anticipated. Furthermore, operational speed and efficiency were initially sacrificed, because insufficient resources were made available to support the merger process, while work on nearly 100 active clinical trials continued.

Similarly, the Group Chairs recommend that, before any further centralization or consolidation efforts occur, the experience and track record of the CTSU be documented to determine how centralization of Group functions through the CTSU has taken place, how the system has been affected (including costs and benefits), and how the strategies should change. Since its first patient was enrolled in November 2000, the CTSU has accrued approximately 3,000 patients in total. Its current monthly accrual rate is 250 patients, for an annualized rate of 3,000 cases, representing 12% of the approximately 25,000 patients that the system accrues annually for therapeutic trials. Because it has not been effective at general enrollment, the Group Chairs recommend that, in the area of patient recruitment, the CTSU should phase out its activities in general enrollment and focus, instead, on serving as the national enrollment catalyst for rare diseases, minority and underserved populations, and trials of drugs whose patent protection has expired.

While the other recommendations in this proposal are being implemented, the Group Chairs propose to undertake a comprehensive six to nine-month study to identify more efficient organizational structures, workflows, and common data platforms to facilitate data acquisition and sharing across the Groups, including the CTSU. As part of the analysis, the Group Chairs will also evaluate the best ways to continue working with patient advocates to develop studies that are relevant and feasible, improve access to trials for minority and special populations such as the elderly, and accelerate the adoption of new standards of care.

2. Adapting the System to the Development of Modern Cancer Therapies

Phase III clinical trials will continue to be required to establish the efficacy of new cancer therapies in the age of molecular targets. These studies will need more carefully selected patient populations and more precise molecular definitions of the disease state, stage, and risk.

The Groups are positioned to adapt to the development and delivery of targeted therapies, because they have the Phase III capabilities and networks to recruit homogeneous populations on a national basis. The Groups also have tissue banks with well-annotated clinical data linked to image archives, which are an integral part of the Groups' science. However, the Groups need better access to core facilities, such as central molecular pathology and reference laboratories, to conduct rapid screening to identify appropriate populations for studies of targeted agents and to

assess pharmacodynamic endpoints. SPOREs and Centers, which could provide such core facilities to the Groups, need financial incentives to support these activities. Consequently, the Groups and Centers require stable funding to develop fresh tissue networks, pay for gene arrays, and fully conduct molecular profiling.

Investigators need access to an inventory of available reference laboratories and their capabilities. One simple way to do this would be for Centers and SPOREs to list their laboratories on an NCI Website that would be accessible to Cooperative Group investigators and administrators. Thereafter, work could begin to standardize the operating procedures across the laboratories. Similarly, the Groups should provide an inventory of specimens and images available in their repositories for use by investigators in Centers, SPOREs and elsewhere. As previously stated, investigators should have access to the system's facilities, including laboratories, regardless of institution.

Correlative laboratory and imaging research (translational research) have been and must remain an essential feature of Cooperative Group efforts. The Groups are the only program within the NCI system that has standardized clinical annotation for large-scale translational research investigations. The annotated tissue banks and image archives are a resource for the public good that the Groups must protect, and which should be made available to non-Group scientists. The Groups need consistent funding, so as not to separate the tissue banks from the Groups' scientific life-blood. For example, the Eastern Cooperative Oncology Group (ECOG) will use tumor characteristics that could be of prognostic and predictive value to stratify patients with Stage II colon cancer to identify those patients at increased risk of recurrence.

Each Group has database legacy systems that surround their clinical, imaging, and pathologic material. Because legacy systems have not been created to handle the development of modern therapies, an opportunity exists to imaginatively develop an informatics platform that would interact with Centers and SPOREs. The biostatistical and data management programs of the Cooperative Groups are based in major Cancer Centers. Consequently, data integration across the system is critical to engender access to clinical and image data by investigators, independent of their institutional affiliation. The Cooperative Groups enter approximately 25,000 patients yearly on therapeutic trials and have about 150,000 patients in active follow-up. As noted above, clinical and image data is intrinsically linked to tissue. The NCI should engage all the biostatistical centers in a dialogue to harmonize Cooperative Group efforts with their bioinformatics initiatives. A good example is the cancer Biomedical Informatics Grid (caBig), whose goal is to help foster data sharing among the components of the system.

The system should take advantage of the Cooperative Group Phase III capabilities that can access large and diverse patient populations, rather than creating new networks or consortia. As part of the six to nine-month study proposed in the previous section, the Group Chairs will make recommendations on how the system could be adapted, including how the Groups might interact with a national image and bio-specimen network, create a system-wide bioinformatics resource, and develop a preferred approach to pharmacogenetics.

3. Establishing Scientific Priorities

Scientific autonomy has been and will continue to be fundamental to the strength of the entire NCI clinical structure (including the Cooperative Groups) and to engaging future generations of investigators. This makes establishing scientific priorities especially important. The Group Chairs believe that the process for setting the scientific agenda could be significantly improved by re-aligning both the Intergroup and peer-review mechanisms with the goals of the system.

Many of the incentives built into the Intergroup and peer-review systems are counter-productive, leading to the development of more trials than might otherwise be necessary. Today, a Group that develops a scientific idea is most likely the only Group to receive credit for the resulting trial during the peer-review process. Consequently, other Groups have little incentive to participate in joint or Intergroup trials, because they do not receive sufficient recognition. This has created a perverse dynamic in which each Group is incentivized to generate ideas and to function as the lead Group, but discouraged from participating in trials initiated by other Groups. Priority trials, therefore, are those that are led by each Group. The Group Chairs recommend that the peer-review system be restructured to reward both scientific leadership and participation in Group trials.

Traditionally, the Group Chairs have delegated much of the leadership of the Intergroup mechanism to their disease committee leaders. An unintended consequence of this delegation is that the Intergroup process has become unaccountable to the Groups. To make the Intergroup process more accountable, the Group Chairs recommend that the Coalition of National Cancer Cooperative Groups oversee the Intergroup process and appoint empowered project managers, reporting directly to the Coalition, to design, implement, and coordinate the major Intergroup activities. The proposed structure and process, together with the creation of congruent incentives and recognition for participation in Intergroup trials, should result in a tighter focus on the most promising scientific ideas and trials.

As the Intergroup and peer-review systems improve, the role of CTEP should change to facilitate the development of studies proposed by the Groups, rather than regulate each protocol. CTEP should not control the scientific agenda nor perform its role in a way that would stifle scientific creativity. This proposed change in role should extend through the protocol development and approval processes, as noted in the next section.

The Group Chairs also recommend establishing national criteria for closing slow-accruing trials. The criteria should trigger discussions in the data monitoring committees about early closure for trials that are not meeting accrual targets. The Group Chairs are committed to undertaking annual reviews of all open studies and to consider closing studies whose enrollment lags expectation.

4. Accelerating Protocol Development

Activating a Group protocol remains a long, laborious, and complex process, involving many steps and multiple layers of review and approval. After the individual Group's Executive Committee has approved the protocol, final system-wide approval can consume an additional 12 to 18 months. After protocols are released by the Groups, they must be approved by CTEP and, now, by the CIRB before submission to the local IRBs. Because all protocols must be reviewed by an institution's IRB, the additional requirement of CIRB review becomes another step in the process, adding six to twelve weeks of delay to the protocol activation process, without contributing meaningfully to trial quality and safety. And, if new agents are involved, FDA approval is also required and collaboration with industry must be negotiated. As this process has become increasingly inflexible, industry's interest to access the Cooperative Groups for evaluation of their most promising experimental agents has diminished.

The CIRB was established as a pilot project at 22 institutions (four of which agreed to have the CIRB as the IRB of record). However, before the pilot project was completed, much less evaluated, CIRB review for all phase III studies was required by the NCI. The hasty expansion of the CIRB pilot backfired, because the vast majority of local IRBs do not accept CIRB review as a

replacement for their own review. Although the Group Chairs support the concept of the CIRB, the Group Chairs want to see the CIRB validated at the pilot-project level, before it is implemented on a national scale.

The development cycle of a recently approved CALGB study demonstrates the issues. CALGB protocol 80203 required 17 months to activation, from July 2002 when the CALGB Executive Committee approved it to December 2003. During those 17 months, the concept was sent to CTEP for approval (five-month review); after concept approval the protocol was developed and sent to CTEP for review; comments from CTEP were incorporated, and the protocol was resubmitted to CTEP for approval. Subsequently, the protocol was sent to the CIRB for comments. The CIRB comments were incorporated, and the amended protocol was sent back to the CIRB for approval. After CIRB approval, the protocol was resubmitted to CTEP for final approval. Because a new agent, cetuximab, is being studied in 80203, the company holding the IND and the FDA also reviewed the protocol.

Delays in protocol activation slow patient accrual. Because completion of pivotal trials depends on speed of protocol development and accrual, needless delays impede the delivery of potentially better therapies from reaching patients. Such delays also discourage industry participation in Cooperative Group trials at a time when the Cooperative Groups are trying to build effective public/private partnerships.

The Group Chairs strongly recommend establishing targets for time to protocol activation and rate of accrual. Within the Groups, the Group Chairs recommend a more interdisciplinary approach that borrows from the best practices from across the Groups. Once the Groups release their proposed studies, the CIRB and CTEP roles and review processes should be modified as follows:

1) Eliminate double-review of protocols. CTEP review should only take place when CTEP holds the IND. When a company or Group holds the IND, then the FDA alone should review the protocol.
2) When CTEP holds the IND for a registration study, all stakeholders – NCI, Cooperative Groups, FDA, industry – should collaborate for rapid review and activation.
3) When CTEP review is warranted, CTEP (like the FDA) should be held accountable for providing a timely review. If after 60 days, a Group has not heard back from CTEP, the protocol should be deemed approved.
4) Scale back the CIRB to pilot project status, until it has proven that it can reduce the time to protocol activation. In the meantime, eliminate the requirement for CIRB approval before protocol activation.

5. Improving Funding

The Armitage Committee Report and the Implementation Committee recommended that the Groups be fully funded at the peer-review recommended level. However, the Groups remain under funded at approximately 50% of trial costs. Moreover, funding does not increase as accruals increase, thereby penalizing those Groups that exceed their accrual projections. Because the Groups' reimbursement levels serve as a contra-incentive to investigators (especially in comparison to industry trials), participation in Group trials by researchers is below optimal, which holds back accruals in Group trials. Approximately one third to one half of all sites accrue more than ten patients annually. These sites account for 80% to 85% of all accruals. Unless reimbursement levels increase, trying to expand the cadre of physicians who participate in Group trials will be futile.

Group investigators and staffs perceive that the system's financial shortfall has worsened, because the demands of the unproven pilot projects and grossly inefficient site visits have diverted scarce resources from their research and increased their workloads. Unfortunately, Group Chairs are constrained in their ability to respond, because the funding mechanism, Cooperative Agreements, limits their discretionary authority and control. The Group Chairs recommend that CTEP facilitate the funding process by providing more flexibility to the Group Chairs in their interpretation of the Cooperative Agreements.

The Group Chairs endorse, in the strongest possible terms, the recommendations for full funding called for by the Armitage Committee Report and the Implementation Committee. In the meantime, until the overall level of Group funding is made proportionate to the cost of the work, the Group Chairs propose that public/private partnerships be activated to help defray the costs of publicly-funded clinical research. For example, CRADAs could be used as a funding vehicle to cover the shortfall between the NCI per-case reimbursement and the cost to the site conducting the clinical research. More importantly, industry trials, whose financial rewards substantially exceed Group reimbursement rates, could provide significant support to the system. The Group Chairs are confident that the Groups can facilitate the cancer-drug development approval process for industry. (The Groups have been the engine for S-NDAs, and the FDA has accepted the Group operating procedures.) For this to happen, industry-sponsored trials conducted in the Cooperative Group networks must be recognized in the peer-review process, and accrual to these studies needs to be credited toward the accrual goals for Cooperative Group sites. As stated in the previous section, industry-sponsored trials should be subject to FDA review only.

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In this proposal, the Group Chairs have identified 25 ways to improve the publicly-funded cancer clinical research system. A common theme of the recommendations involves correcting misalignments in the incentives, review processes and review criteria so that they support, not undermine, the Mission of the system. The recommendations affect five areas that are crucial to the system's ability to save lives and advance the standards of care for cancer patients. Each recommendation is important; cumulatively, they have the potential to create breakthrough improvement in the performance of the system. The recommendations are summarized on the next page.

The Group Chairs look forward to discussing this proposal with the NCI Director on March 17 and to jointly developing a plan to realize the benefits to be derived from implementing these recommendations.

SUMMARY OF RECOMMENDATIONS

Streamlining the System

1) Harmonize the guidelines for Centers, SPOREs, and Groups to encourage more cooperation; include patient advocates.
2) Modify the peer-review criteria to encourage collaboration and eliminate disincentives to cooperation among the programs.
3) Remove barriers to participation of investigators, regardless of institutional affiliation.
4) Understand and apply the lessons from the COG merger.
5) Conduct a study to determine the best organizational configuration, workflows, and common data platforms to facilitate data acquisition and sharing across the Groups.
6) Document the CTSU's track record. In terms of patient accrual, limit its role to serving as the national enrollment catalyst for rare diseases, minority and underserved populations, and trials of drugs whose patent protection has expired.
7) Enlist patient advocates to improve trial design, access, and adoption of new standards of care.

Adapting the System

1) Use the Groups' Phase III capabilities (access to large and diverse populations; clinical annotation for translational research). Do not create new networks or consortia.
2) Provide appropriate incentives for Centers and SPOREs to function as central laboratories for Group trials.
3) Establish an inventory of available laboratories and their capabilities that all investigators could access.
4) Retain the tissue banks as part of the Groups, and adequately fund them.
5) Develop an integrated informatics platform with Centers and SPOREs.

Establishing Scientific Priorities

1) Improve the peer-review and Intergroup processes to support the system's goals, by rewarding both scientific leadership and cooperation.
2) Appoint the Coalition of National Cancer Cooperative Groups to oversee the Intergroup process through empowered project managers reporting directly to the Coalition.
3) Establish national criteria for closing slow-accruing trials; review trials annually.
4) Change the role of CTEP to facilitate, not control, the generation of ideas.

Accelerating Protocol Development

1) Establish targets (timelines and measurements) for protocol development. Success to be measured by time to activation and rate of accrual.
2) Eliminate CTEP review when CTEP does not hold the IND.
3) When CTEP holds the IND for a registration study, all stakeholders should collaborate for rapid review and activation.
4) Establish that CTEP provide timely reviews of ideas and protocols.
5) Scale back the CIRB to pilot status until proven. In the meantime, eliminate the requirement for CIRB approval before protocol activation.

Improving Funding

1) Fully fund the Groups.
2) Provide more financial discretion and flexibility to the Group Chairs.
3) Modify the peer review process (including sites visits) to make it more cost-effective.
4) Promote public/private partnerships to help fund the system. Ensure that the peer-review mechanism and the regulatory process support partnerships with industry.

Chairman TOM DAVIS. Thank you very much.

Ms. Stovall, thanks for being with us.

Ms. STOVALL. Thank you, Mr. Chairman. Good morning. I am Ellen Stovall, president and CEO of the National Coalition for Cancer Survivorship, and I am a 32-year, two-time survivor of cancer.

NCCS is the Nation's oldest survivor-led organization for people with all type of cancer. Our mission is to advocate for quality cancer care for all Americans, including the 10 million cancer survivors alive today in this country.

I'd like to thank you for the opportunity to testify to the important work of this committee.

I have a very direct and personal experience with cancer clinical trials. When I was first diagnosed in 1971, I actually started treatment on the day that President Nixon signed the National Cancer Act. My father literally thought I would be cured in 7 years, as the whole world would be, of cancer. Unfortunately, I was unable to participate in a cancer clinical trial promising a new therapy for the type of Hodgkin's Disease that I had because I was deemed ineligible for the trial, as I had just had a baby. Today, that therapy has become the standard of care for Hodgkin's Disease, and when I was re-diagnosed with the same disease 12 years later I was able to take the drugs that had been in that clinical trial some 12 years earlier, so I really do understand the progress that is made through clinical research.

I cite this experience to draw your attention to two key issues: first, restrictive standards for trial enrollment unnecessarily prohibit many patients from entering a trial; and, second, clinical trials do serve as the means of testing new therapies and moving the standard of care forward step by step, extending or even saving many lives that would have been lost to cancer.

There are many reasons why the rate of participation in trials is low. Both physicians who enroll their patients in trials and those individuals who agree to receive their care in a trial encounter several barriers to participation. All of those obstacles must be addressed if we are to improve the clinical trial system.

The community has made great strides in increasing the awareness that care in a clinical trial may, indeed, be the best treatment option for a cancer patient, but our educational mission is incomplete. We still have to address the fears of some regarding the risks associated with trials, as well as the reservation of others about the value of trials. This is perhaps most acutely felt in under-served communities where socioeconomic, cultural, ethnic, and language disparities present even more barriers. Cancer patients may have to make sacrifices to enroll in a trial, and they want to believe that their time and energy are well spent in a valuable research endeavor.

Over the last several years, some researchers and companies have taken the step of involving advocates early in the clinical trial design process. The FDA has also made great progress, particularly in the last few years, of involving advocates at earlier and earlier stages of drug development. Those efforts have generally been rewarded because advocates have embraced those trials and encouraged participation in them. Examples of this are breast cancer advocates' involvement with the design of the hterceptin®, trials, and

multiple myeloma advocates' involvement more recently with trials for Velcade®. For more than a decade, NCCS and a number of other patient advocacy organizations and professional societies like ASCO collaborated in a legislative effort to address the failure by third party payers to pay for the routine patient cost in trials. After many years of unsuccessful legislative effort, we were able to persuade the Clinton administration to issue an Executive memorandum instructing Medicare to allow all beneficiaries, those with cancer as well as other life-threatening diseases, to participate in high-quality clinical trials such as those sponsored by Federal programs or under the oversight of FDA. With this change in the leadership role of Medicare in health policy, reimbursement has seemingly become less of an obstacle.

While cost is a primary concern, of no less concern is the fact that so few doctors recommend a clinical trial for their patients as a viable treatment option. Clinical research is expensive, requiring an extensive infrastructure both at the central point of control that is the research centers providing overall management of the trial and at the level of the individual provider. Research requires sophisticated, dedicated personnel such as research nurses, as well as the means for data collection and management, not to mention additional time commitment from physicians involved.

For many years, cancer clinical researchers have made clear that the rate of payment from NCI for their participation is inadequate, despite some modest increases over the last few years. Privately funded research has overtaken that sponsored by NIH and other Federal sources because industry is willing and able to pay the full cost of research, whereas the Government's funding lags behind.

As you probably know, over the last two decades cancer care has truly moved into the community. As much as 80 percent of cancer care is provided by community oncologists around the country. This system has been welcomed by cancer patients who prefer to record their care near their homes, thereby avoiding the dislocation that occurs if they must travel. Obtaining care in the community does not eliminate a patient's ability to receive care in a trial. As we just heard from Dr. Comis, as many as 60 percent of clinical trial enrollees are referred to trials by community doctors.

The fact remains that only a small percentage of adults are enrolled. We are hearing disturbing reports from community oncologists that, as a result of changes in Medicare reimbursement for cancer care that were included in the MMA, they may be forced to reassess their participation in clinical trials altogether. The MMA reformed the system of payment that was over-paying for chemotherapy drugs, a reform that we all agree was necessary. The bill also made a temporary adjustment in the payment for expenses associated with delivering chemotherapy, but the concern of all of us who care about quality cancer care is that in 2005 this new law will reduce total payments to cancer care that such an extent that services offered by the community oncologists will have to be reduced, and clinical trial participation may be among the first things to go.

We often describe the system of cancer care in the United States as the best in the world, and yet a series of reports from the Institute of Medicine's National Cancer Policy Board proclaimed great

inconsistencies in the quality of care and the lack of any systematized way of assuring access to it. We do know that a good deal of this disparity could be corrected if more people were involved in clinical research and were assured access to a high quality clinical trial as a matter of first course rather than last resort.

Our country is unusual in our ability to provide high-quality care, including care in a trial in a community, but the system is suffering from so many strains that I fear all these factors will create such a stress that it may be impossible to carry on clinical research in the future that people could have access to.

NCCS and others have been engaged for more than a decade in efforts that will ensure that clinical trials are an integral part of cancer care in this country. We are dedicated to that outcome, and we look forward to cooperating with this committee and others in ensuring that it continues in the future.

Thank you.

[The prepared statement of Ms. Stovall follows:]

STATEMENT OF ELLEN L. STOVALL
President & CEO
National Coalition for Cancer Survivorship

ON CANCER CLINICAL TRIALS
BEFORE THE
HOUSE COMMITTEE ON GOVERNMENT REFORM
MAY 13, 2004

I am Ellen Stovall, President and CEO of the National Coalition for Cancer Survivorship, or NCCS, and a 32-year two-time survivor of cancer. NCCS is a survivor-led advocacy organization for people with all kinds of cancer; our mission is to achieve quality cancer care for all Americans. Since its founding in 1986, NCCS has recognized that access to clinical trials is a major component of quality cancer care. We are extremely pleased that the Committee on Government Review would focus its attention on the achievements and shortfalls of the federal government's support for clinical cancer research, and we hope our perspective will aid the Committee in recommendations for change.

A quick review of the NCCS web site at www. CancerAdvocacy.org reveals the importance of clinical trials to cancer survivors as well as the central role of various government agencies and government-funded academic entities in organizing and conducting these trials. What is less obvious is the growing—and indeed now preeminent—position of private industry in planning, funding and carrying out cancer clinical trials. This development is not necessarily unwelcome, but it does raise questions about the appropriate balance between public and private investment in research. If we believe as a society that there is a role for the federal government in the clinical research enterprise, then we should pay special attention to challenges confronting that involvement, and this Committee is well placed to conduct that inquiry.

There are no doubt many reasons why the rate of participation in cancer clinical trials is much lower than we would wish. For a long time, those of us involved in cancer patient advocacy felt that the problem was one of education—that is, people were not adequately informed of the benefits, both to the individual patient and to society, and were excessively focused on the risks of research participation. It is still true that some may be discouraged from enrolling in clinical trials because of rare but nevertheless troubling media reports of unethical conduct by researchers, but for the most part we believe that organizations like ours and many others referenced in our web site have gotten the word out that clinical trials are a positive, both for the patient and for the sake of medical progress. With widespread internet access and many educational outlets on the web and otherwise, cancer patients and their families should now be much better informed about clinical trials.

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Another issue of concern for many years was the tendency of third-party payers, including most prominently the Medicare program, to disallow coverage of routine patient care costs for patients participating in clinical trials. The rationale for this unenlightened policy was that clinical trials were by definition "experimental" and thus excluded from most insurance coverage. Various legislative proposals during the 1990's sought to change the policy, particularly for Medicare, but these did not prevail, mostly for reasons of perceived cost. Fortunately, we were able to persuade the Clinton Administration to issue an executive memorandum instructing the Medicare program to allow all beneficiaries, those with cancer and also with other diseases, to participate in high quality clinical trials, such as those sponsored by federal programs or those under the oversight of the Food & Drug Administration. With this change, and the leadership role of Medicare in health policy, reimbursement has seemingly become less of an obstacle than before.

Cost remains a primary concern, however. Clinical research is expensive, requiring an extensive infrastructure, both at the central points of control—that is, the research centers providing overall management of the trial—and at the level of the individual provider. Research requires sophisticated dedicated personnel, such as research nurses, as well as the means for data collection and management, not to mention additional time commitment from physicians involved in the research. One of the reasons why privately-sponsored research has overtaken that sponsored by the National Institutes of Health and other federal sources is that industry is willing and able to pay the full cost of research, whereas the government's funding seems to lag behind. Despite some increases in per-patient payment by the National Cancer Institute, the NCI payment falls far short of covering the actual per-patient cost.

At the same time, trials sponsored by NCI seem to be burdened by unnecessary duplicative review and bureaucratic control by the Cancer Therapy Evaluation Program, or CTEP. I understand that the cooperative research groups are developing recommendations to streamline the review process at NCI and to facilitate collaboration with industry funders. Another source of unnecessary duplication and cost is the numerous reviews conducted by the Institutional Review Boards, or IRBs, at local institutions participating in multi-site trials. The duplication of review clearly adds to the overall costs of the research enterprise, but it also contributes to delay—delay in commencing trials, delay in getting results and delay in medical progress. The American Society of Clinical Oncology, or ASCO, will be convening a large meeting of federal officials, academic and industry scientists, and patient advocates later this month to attempt to address this problem in a constructive manner.

All of these factors tend to make the cancer clinical trial process much less efficient and user-friendly than should be the case. I fear, however, that the situation is about to become much worse by virtue of changes in Medicare reimbursement mandated for next year by the Medicare Modernization Act, or MMA, enacted by Congress last year. Congress had been concerned for many years about the "profit" that physicians made through the spread between the Medicare payment rate, based on an inflated "average wholesale price," or AWP, and the actual cost of the drugs used to treat cancer and other diseases. My organization and most others interested in cancer sought to reform this system, but the fear is that the MMA solution adopted by Congress will reduce total payments for cancer care to such an extent that services will have to be reduced, and clinical trial participation may be among the first to go.

During 2004, total payments for cancer chemotherapy are maintained at roughly the same level as in the past by simultaneously reducing payments for drugs and increasing payment for services by an additional 32%. In 2005, however, drug payments will be reduced even further—perhaps to the point where individual physicians may not be able to purchase drugs for the amount Medicare will pay—and the "add-on" will be reduced from 32% to 3%. Then, in 2006 and thereafter, the additional payment for services disappears entirely. The Congressional Budget Office has estimated that drug payments will fall by $300 million in 2005, and payment for services will decline more than 20%. Some speculate that the total reduction could amount to 40% of current levels. As another measure, the CBO has scored savings in excess of $1 billion per year over the next 10 years resulting from these provisions.

For most oncologists, clinical research is a cost, not a profit, center. It seems inevitable that payment reductions of this magnitude will make it extremely difficult for oncologists in private office-based practice (which is where most of the nation's cancer care and most of the cancer clinical trials occur) to continue the investment necessary to enable them to offer clinical trials as an option for their cancer patients. In fact, this fear is confirmed by surveys conducted by ASCO, the leading oncology medical society.

A survey of domestic ASCO members prior to enactment of the MMA legislation reflected that reimbursement changes like those that were eventually adopted would lead to the following results:

- 73% of practicing oncologists would send cancer patients to a hospital for cancer chemotherapy rather than treating them in an office setting;
- 53% would limit the number of Medicare patients they treat;
- 42% would stop conducting clinical trials in their offices; and
- 44% (55% of those over age 55) would plan to retire from practicing medicine earlier than anticipated.

A second ASCO survey is of even more interest because it was directed not to office-based practitioners but to cancer centers that would not be directly affected by the reimbursement declines. Surveying 20 national cancer centers, ASCO found a degree of concern commensurate with that of physicians in private practice. Among the responding centers, 70% concluded that such legislation would affect their operation "a great deal." With respect to clinical trials, three-fourths of the centers felt their program would be scaled back, with a third of all responders saying that clinical trials would be scaled back to a large degree.

Thus, from two very different cohorts of cancer providers, the view seems entirely consistent: reimbursement changes of the sort that were enacted by Congress in the MMA legislation would likely cripple clinical research, with most believing there would be an adverse impact on clinical trial enrollment at both the individual physician office and the cancer center. Across the spectrum of cancer clinical trials, the pullback will be substantial and potentially irreparable.

Today, we can be proud to have the very best cancer care in the world, and our cancer clinical research is second to none. But a great threat is looming in the form of unreasonable cuts in payments for total cancer care, which surveys show will inevitably affect not just individual patient care but also longer-term progress against the disease. If something is not done, and done soon before these reimbursement cuts take effect in January 2005, I fear that the damage will irreparable and that we as a society will be paying for many years to come.

The charge to the Committee on Government Reform could obviously be far-ranging with so many problems confronting the cancer clinical research effort, but none is more immediate or fundamental than the threatening Medicare reimbursement cuts, which will take effect next January if legislative or administrative relief is not forthcoming. I hope that you will consider analysis of this issue and recommendations for prompt action to be priorities of the Committee.

Chairman TOM DAVIS. Thank you all very much. I think the committee has some questions, so I'll start with Judge Carter.

Mr. CARTER. Thank you, Mr. Chairman. And I thank all of you for being here. Ms. Stovall, please don't be mad at me for what I said about Lance Armstrong, but it was a shock to me to realize that the definition of a survivor was survive each time, and as you pointed out in your testimony, you said, "I'm a two-time survivor." To me a survivor is it's all over and it won't happen again.

Ms. STOVALL. It would be nice if that were true.

Mr. CARTER. Yes, and I think that's the goal we are looking for. And a question I also have, I question what's going on, and maybe you can give me an answer. It seems to me that the research that we're doing in the areas of cancer is how to fight the tumor. Do you know, in these clinical research experiments that are being done, are we doing anything to inoculate for cancer, to come up with a genetic engineering to fight cancer? Are we still in the same direction we were in 1970, how to fight a tumor? Does anybody know the answer to that?

Dr. PECORA. I'm happy to comment on that. I think it is two-fold. I think, one, and sort of a generic way of speaking, is there is a focus to make the tumor go away, and that's a lot of giving medicines, doing surgery, radiation, but I think there is a growing and equal emphasis of keeping it from coming back and understanding how and what you need to do.

You're right. I mean, there are strategies now aimed at using certain approaches to make tumors go away and then using cancer vaccines as an example to prevent it from coming back. When you have therapies that are only of modest benefit, you do the best you can. There are a whole new class of agents now—you heard about them this morning—that's changing the whole cancer paradigm that I'm not even sure how to answer that question, because it may be you don't need to make the tumor go away and the person could have a happy and healthy life, like Glevic that you heard about. It doesn't cure CML, but it makes that clonive cell go away for a very long period of time, maybe forever.

So the answer to that question is changing, but I do think your concern about keeping it from coming back is on the minds of people who do this sort of thing.

Mr. CARTER. You know, one of the things, just human nature—and I have no expertise in this at all, just human nature and comments—in Texas MD Anderson has a great reputation in Texas. Anybody that has cancer in Texas will try to go to MD Anderson Hospital. I'm sure there are people at Brackovitch Hospital in Austin, oncologists that can do a great job in treating. That's the publicly perceived—it is perceived all the way—it's really a private hospital now—it is perceived by the people in Austin to be a public hospital because it was at one time our public hospital. If given the choice, they will go to MD Anderson, which is funded heavily by public funds, and it is perceived to be a great scientific research center, a private hospital, if you will. It is perceived that way and everybody would want to go to MD Anderson because they think they have success.

I think that's part of what your clinical trial situation is. People perceive this as another Government program rather than—do you

get my drift? When you're talking about the National Cancer Institute, well, they've been at it for 50 years with $52 billion worth of money spent. They're just another Government program. And if I can go to MD Anderson and participate, that's fine. In fact, I think MD Anderson actually runs some of your programs. But do you understand? It's the public perception.

I would be willing to bet we have a better turnout at MD Anderson in Texas than you would some place else. I'd be willing to bet the farm on that. So a whole lot of what you have is the public perception that Government is failing in the war on cancer and that it is going to take private involvement to succeed in the war on cancer.

Dr. PECORA. Well, I did make a statement that I will stand on. I think that the Government side of the equation can be more efficient, and I think that it takes too long to get things through the process, and I think we have created a bureaucracy that you heard about that is impeding discovery and making it harder to do.

I've learned more in the last 2 years as a cancer administrator than I ever learned as a cancer investigator about why we're not getting more people into clinical trials, and many of them are business issues. They're not science issues. These are the things that—one of the reasons I wanted to come here today was to address this with Congress, because you fund these efforts. So I think if you—the money for you is to look at these things and to try to drive efficiencies into the system.

Mr. CARTER. Absolutely, and that's one of the reasons I mentioned it to the last panel about the intellectual properties issues. The incentives—and let's face it, we live in a world where we're all trying to make a living, and the incentives to go out and meet these challenges and advance private capital in meeting these challenges, in my opinion, needs to be encouraged. The Government can't fight this war forever. We fought it and we can use some help, I guess is what I'm saying.

Dr. PECORA. There's one other thing I want to say before—I don't want to monopolize the microphone, but another misnomer, this concept of clinical research, people hear "research" and it has all these connotations that we heard one of the Congressmen speak to before. In cancer care, when the outcome is dismal, clinical trials should be the standard of care, not that there's something better and they're trying this out. I mean, that's a bad way of looking at it, particularly when the likelihood, as we get smarter about the mechanisms of the disease, how to read if something is effective or not are improving at light speed. The likelihood of you having a better outcome by participating in trial is going to go up proportionately.

So what we need to do as a Nation is to push cancer trials out into the community offices, into the hospitals that aren't the MD Anderson's of the world, because that's not where all patients are treated. That's where the minority of patients are treated.

Mr. CARTER. That's right.

Dr. PECORA. We have to get this in the doctors' offices, and in order to do that we're going to have to support them. We're going to have to provide them funding for research nurses, data man-

agers, and we're going to have to simplify the process or it is not going to happen.

Mr. CARTER. We're going to have to convince the public's perception that they'll get that equal treatment in that doctor's office that they would get in this famous—supposedly famous cancer center. And that's the perception you've got to overcome on these clinical trials, in my opinion.

My time is up. Thank you, Mr. Chairman.

Chairman TOM DAVIS. Thank you very much.

Mr. Garrett, would you like to ask any questions?

Mr. GARRETT. Thank you. I appreciate the testimony of everyone.

A couple of quick questions. First of all, with respect to New Jersey and on the insurance side of the issue, you indicated how you were able to convince the insurance industry to provide coverage for the expenses of clinical trials. How did you do that? What is the status nationally, if you know? And what is the recommendation as far as facilitating that on a national basis?

Dr. PECORA. Well, how we did it in the State is we got the major cancer program directors and people involved in various aspects of clinical trials to come together in a forum and we brought in the CEOs and other representatives of the insurance industry and showed them the data. We made the claim, "Look, you know, you're paying for things that are marginally effective. Wouldn't you want to pay for something that could be better for your subscriber?" And they got it. And they got it to the point where they did it voluntarily.

I can't speak to the rest of the Nation. I know there's efforts around the country, but I'm not privy to that information.

Dr. COMIS. Maybe I can help clarify. This is a very complicated issue. In the Harris Survey that I mentioned before we asked several questions about personal barriers to participation—travel, taking time off from work, insurance coverage, etc.—and the thing that was on the very top of the list, 60 percent of the 6,000 cancer patients that we surveyed said that they were afraid their insurance companies wouldn't pay.

Then we went to the 4 percent of patients who did actually participate and asked a final question which was: in the end, did your insurance company pay? And 86 percent said yes.

Now, how hard it was to get there we didn't ask, or how difficult it was to navigate the system, but this insurance barrier issue is a major perception barrier, at least, and there are now—Ellen may know the exact number. I think there are 19 States now that have legislative solutions, there are about three States that have nonlegislative solutions. Medicare said they would pay. I think it is incumbent on us, and this is what we try to do in a lot of our materials is to get the word out that, in fact, your insurance companies have said that they would pay, that States are backing you, and if you are having trouble you have to use that information to make sure that you have access to clinical trials.

Mr. GARRETT. And, following upon this, then, if I may, Dr. Comis, you made the comment—and you did, too, Andy—as far as the responsibility of greater education, but to me isn't the education responsibility on the part of the doctor, the oncologist? Isn't he supposed to know this, and isn't he the one that's supposed to

convince the patient that clinical trials are necessary and, if he has been in the practice for a while, that he should know the statistics that he can rattle off that he can put his patient at ease?

Dr. PECORA. Right. Well Mr. Carter I think hit the nail on the head. It is very hard to battle public perception. I am a practicing physician. I see cancer patients. I still put people on clinical trials. I do it every day, and it is hard. And the reason it is hard is because people come in with preconceived notions, and the minute you start talking about a clinical trial all of the sudden warning bells go off.

You know, we have high-profile cases in our country, the Jesse Geisinger case, going back historically to the Tuskegee experiment, the whole concept of what IRBs are doing now. It is, I think, pushing people in the general direction of being suspicious and having a bias against clinical trial, and I don't think at the individual physician level that's going to be reversed very readily. I think it has to be a societal issue.

Dr. COMIS. Maybe I can followup on that, because we've studied this a lot. I agree totally. In the end, it's the interaction between the doctor and the patient that decides when somebody goes on. And, in fact, I mentioned in my remarks that only 15 percent of the patients in the survey were aware that they could participate, 85 percent weren't.

If you look at the people who were aware, a quarter went on. And if you look at the difference between the quarter that went on study and the three-quarters that didn't, it was all the doctor. The doctor helped educate them about trials, helped find a trial for them. The doctor and the staff worked on this together.

I agree. There are two components on how we have to approach this. One is to increase awareness and decrease misconceptions on the part of the patients and the public, but the other thing is to facilitate the involvement of the doctor in the process.

You know, it's not just reimbursement. It takes time. It takes staff time, patient time to do this, and we have to get the resources out to the sites, particularly the community sites that are really committed to do this, and the resources are not there and the challenges are great.

Ms. STOVALL. And I just want to add that, you know, I put a lot in my testimony, my submitted testimony, about physician reimbursement issues which, Mr. Chairman, you touched on, and it is not about the income of doctors or what doctors make, it's about how we value the time they spend with their patients and their families. When we have been over-paying for the chemotherapy that they provide and grossly under-paying for the time that they spend counseling families and patients about treatment decisions which are more and more complex as time goes on with the new science, I think that we really have to look at our reimbursement system and put the dollars where we value the doctors' time.

Mr. GARRETT. Thank you.

Chairman TOM DAVIS. Thank you. Thank you very much.

Mr. Duncan, do you have any questions?

Mr. DUNCAN. Well thank you, Mr. Chairman. Thank you for calling this hearing.

One thing I'm curious about, I have read in the "Wall Street Journal" and other places sometimes that it takes—I've seen figures of $650 to $850 million to get a typical drug approved in this country, and it sometimes takes 10 or 12 years, and I've also read that in no other developed nation does it take anywhere close to as long. I remember the "Wall Street Journal" had on its front page several years ago this small company in Illinois had a breast cancer detection pad that had been approved in every other country where they had asked for approval, most of them within days or weeks, but they had been—I think it was 9 years, and they still weren't approved in this country, and they had some quotes from cancer specialists saying that thousands of lives have been lost because that had happened.

I'm just wondering. I assume that none of you can say anything critical about the FDA or maybe they'd get back at you later, but are we doing any better on any of that stuff? Why is it that it takes so much longer and so much more money to get approved here as compared to any other developed nation? I mean, you can go overboard on anything, and I'm just wondering about all that.

Can any of you say anything——

Dr. PECORA. I'd like to comment on that.

Mr. DUNCAN [continuing]. Without getting in trouble?

Dr. PECORA. Well, you always get in trouble.

Mr. DUNCAN. OK.

Dr. PECORA. But I do think that the FDA talked a little bit about this critical path document that they put out, and personally, as someone involved both on the academic side and on the corporate side, I find them getting more and more user friendly, and I do think that some of the initiatives will decrease time to discovery and cost to discovery, particularly as we get better at screening for toxicities and putting the right kind of people on trials, i.e., people who have the potential for benefit.

But I see the major stumbling block becoming this issue about clinical trials. This is not going to go away. This is going to get worse. People in the community, people who are doing this, you're not going to answer a question of whether or not something is safe or effective until you test it on a person, period. And until we fix this system, which is going in the wrong direction, that's going to maintain that high cost of discovery, the 10- to 12-year timeline. You heard plenty of testimony today to attest to that, and I think that's where the emphasis should be now.

Ms. STOVALL. I just want to add on to that. I mean, I remember Dr. Pazdur, who was on your first panel, remarking at several meetings over the last few years that we've attended that when a really good drug, a really novel therapy comes to the FDA, you see it move very, very fast. I don't know what that means if they're not exciting therapies that are coming to the FDA what the countervailing point would be. But I do know that the FDA—the burden on the FDA in terms of peer review capabilities, well-trained specialists to review oncology products is just not what it needs to be in terms of capacity building. I think that's another area for this committee perhaps to examine in its future deliberations. I think that would be a very interesting thing to pursue.

Mr. DUNCAN. Well, what happens? If it takes, you know, hundreds of millions or years to get a drug approved, then obviously what you do—this is one of the main reasons why the drug industry has ended up in the hands of a few big giants, because a small company can't handle that. And then also the small companies don't have the connections within the FDA. Chairman Burton said in here one time that 9 out of the last 14 FDA commissioners work for the big drug companies now. I don't know if that's true or not, but, boy, there just is a lot of things going on apparently that—I mean, people wonder why drugs cost so much, and that's—this seems to me to be why. It is our own—we've let the Government get too big and too bureaucratic, and if we don't cut this down a little bit and speed this process up and make it where a small company has a chance again, these drug prices are just going to go up even more, it seems to me.

Thank you, Mr. Chairman.

Chairman TOM DAVIS. Thank you very much.

Let me just try to wrap a few questions up. First of all, let me just pick up on where Mr. Duncan left off. If there's one or two things Government could do to really help this process along, would it be the funding dollars, would it be speeding up the regulatory process, would it be reducing the paperwork and the bureaucracy that you have to go through and patients have to go through, would it be information dissemination? Let me start, Ms. Stovall. You've taken a leadership role on this from the patients' perspective. From your perspective, what do you see? And then let me ask everybody what they see from their perspective. We're talking about Government's role. So much of this is private.

Ms. STOVALL. Well, I think as patient advocates we do look to Government and the very, very important role of both the FDA and the NIH and CMS, frankly, play in this whole, you know, landscape of both developing new drugs, the research approval, and then finally paying for them and getting them to people.

I would like to see better coordination among these agencies, working more collaboratively, having some of the regulatory barriers removed, having a bit of a more transparency to the FDA processes that I believe could truly make things work better, better training of reviewers, more attention paid to that whole process, including I think something that has been mentioned but largely not examined very closely, and that is institutional review board reforms, because I think the regulatory burdens on the system, as Dr. Comis and others have mentioned, are at this point very onerous, and really helping lawyers more than they are helping patients succeed in getting these new therapies.

Chairman TOM DAVIS. I like that one. That's not even, I mean, that's something that is within this committees jurisdiction and is not even big dollars. It's just trying to be efficient with what we do.

Ms. STOVALL. It's just making more efficient the things that we already have in place, because I do think that the protections that Government offers are very important to patient care but shouldn't be burdensome.

Chairman TOM DAVIS. Thank you.

Dr. Comis, do you have any thoughts on that?

Dr. COMIS. Yes. I would followup with three areas. One is I think the Government—the NCI has to recognize that it needs to fund these things at an acceptable level, at a level it can be done. For the group system, $150 million out off a $4.3 or $4.4 billion budget, I mean, that's like chump change. So, I mean, people have to decide whether they want the Government to be involved in this. And they have to be, because we can ask questions that a company can't.

The second thing is we have to be able to interact and develop relationships between the public side and the private side. The private side has developed all the drugs, and we have to be able to work with them very, very effectively, and there are a lot of barriers to that need to be broken down.

As well, I think that the layering of the Government bureaucracies have to be harmonized between FDA, NCI, etc.

And, last, I'd followup with one other huge thing that could happen, and it does relate to the OHRP, the regulatory office. If that office wrote a letter to the 1,600 IRBs that we deal with tomorrow and said, "We will accept the recommendation of the central IRB that has been sponsored by the NCI," that would open up the whole deal.

Those three things could really make a huge difference.

Chairman TOM DAVIS. Thank you very much.

Dr. Pecora, any thoughts?

Dr. PECORA. Yes. It's somewhat repetitious, but for the Government which funds all of these efforts to take a product development, like you want to make a product mindset, and look at all of the issues that we've discussed and see where Government can intervene in a way that continues to protect patient safety, continues to protect patient privacy but gets rid of the bureaucracy and the inefficiencies, centralizing IRBs, getting rid of the craziness we have with the way we do adverse event reporting, and there's a list of things that I don't want to repeat in the interest of time that can and should be done.

Chairman TOM DAVIS. Well, let me ask you this. Do you think that the central IRB that has been developed by the National Cancer Institute has proven to be effective in eliminating duplicative applications in the review process?

Dr. PECORA. I think it will. I think it has been and I think it will, and I think centralization of IRBs in the country would be wonderful.

Chairman TOM DAVIS. Well, let me just ask this. In terms of getting the doctors involved in this, because that's really your pressure point here—people get diagnosed by their doctors. What are my options? What's the best way to get that? Is continuing medical education an option here for oncology? You do an hour talking about what is involved here, what are the options, how they can counsel patients? Or is there a better way to get that word out? Because it seems to me if we do a better job of that, we're going to have plenty of people lining up to be part of these trials.

Dr. PECORA. It will only happen if you match that with the resources they need to do it, and they don't have it right now.

Chairman TOM DAVIS. OK.

Dr. COMIS. But I also think that—you know, I mentioned in the body of my talk that the Coalition or the Cancer Cooperative Groups are working closely with ASCO, the American Society of Clinical Oncology, in education. You know, I think that we have to—you know, ASCO is perfectly positioned to try to take the lead in this educational process along with us, and, in fact, there have been some innovative approaches with regards to recognition awards at the annual meeting, and also with we're developing a series of meetings to try to have the 25 or 30 percent of the practices that are really great at this educate the people who are really interested but can't see a way how to do it. And over the course of the next 3 years we hope to have several meetings and a syllabus that arises from that.

I think we have to focus on the doctors who are interested in doing this but don't seem to have the wherewithal to do it, but it can't be done without resources.

Chairman TOM DAVIS. Ms. Stovall, let me ask you—you answered that, but also, as you look around and you network with patients and so on, are we seeing any geographical issues on this, as well, or any demographic issues in terms of who is getting notified, who sees the options, and who is lining up?

Ms. STOVALL. Well, to answer your last question first, I really think that if you looked at the map that Michaele Christian put up originally with all the dots on it about where places are funded to do the work, there's a big gap right in the middle of the country where there aren't too many dots, and this represents a lot of farmland, it represents a lot of rural America and a lot of poor people.

I want to add on to that the disparity again is created both in the inconsistency in the way treatment is provided and offered to patients, but also the health care disparities. The uninsured and under-insured are terribly disadvantaged by not having access.

I really think that the point again, building on what Bob just said about physicians, physician education, training, all of that is wonderful. If we do not fix the reimbursement system that's being dismantled with the current MMA, we really are going to see even more disparity in care than we are seeing now. And that's not just with clinical research, that's with all kinds of treatment, because doctors are just going to go out of business, and it is just a pure and simple fact.

Chairman TOM DAVIS. And that's a problem——

Ms. STOVALL. It's a serious problem.

Chairman TOM DAVIS [continuing]. Across the medical field. It's not just here, it's everywhere.

Ms. STOVALL. Right.

Chairman TOM DAVIS. You get the Government buying so much health care, and that's how we think we save money.

Let me ask you this, too. Has the FDA's accelerated approval, their expanded access, priority reviews, and fast track policies—do you think they've approved and shortened the length of the approval process as a whole? And do patients receive drugs and therapies more quickly under these policies? Or do you think it is just a lot of rhetoric?

Ms. STOVALL. I have seen improvement, and I think it is because I know that patient advocates are actually in there and they are

involved and they are constantly putting pressure on, as well. They have the most to gain or lose from what happens with new therapies that come through the FDA. So I would say yes, there has been improvement, and I think particularly under Dr. McClellan when he was there and Dr. Pazdur specifically we saw tremendous improvement.

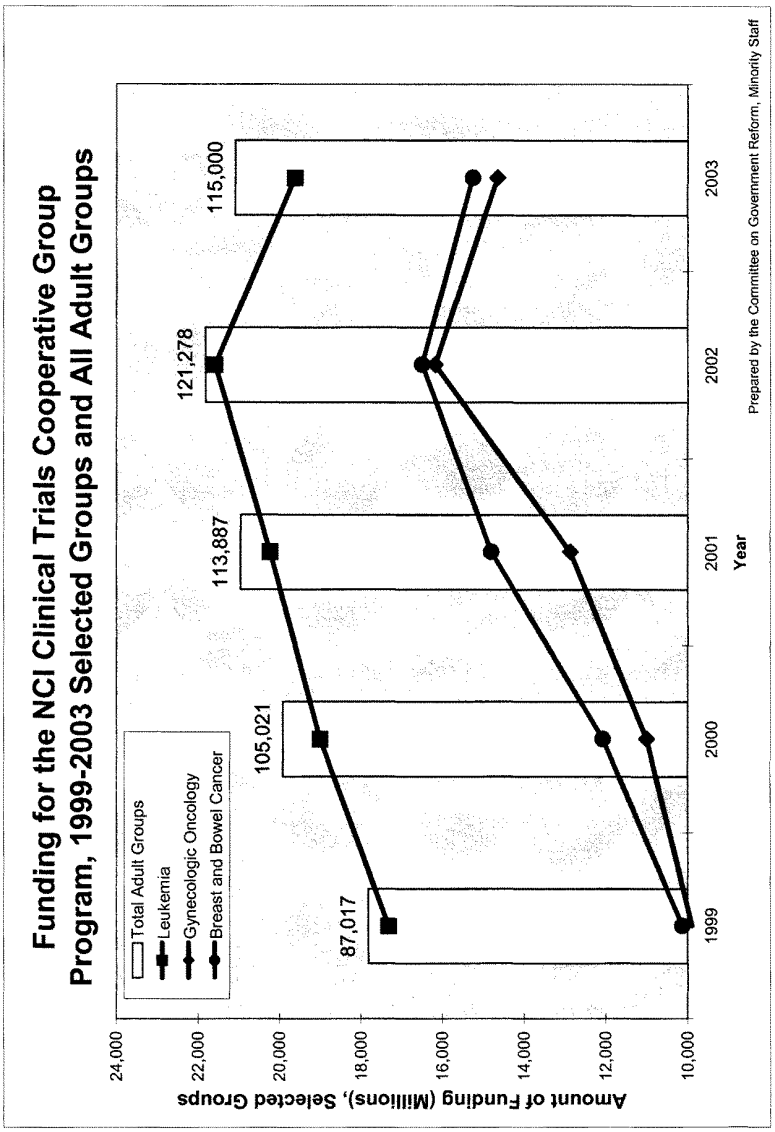
Dr. COMIS. I agree with that, and I think that the drugs that appear active are getting in the hands of the physicians and patients quicker, and I think that most as importantly, you know, we're regulated by two bureaucracies, the NCI bureaucracy and the FDA bureaucracy, and we need to harmonize those things and, in fact, Rick Pazdur and Michaele and those of us from the extramural environment are working on trying to do those things. So it will be very, very important to facilitate this interaction between the public side and the private side of the system.

Chairman TOM DAVIS. Well, let me say to all of you thank you for, first of all, your testimony. I think it has been very, very helpful to us. I hope it has been helpful to the previous panel, as well, as they take notes on this and try to improve and see what we can do about it. But I also thank you for what you're doing in the fight against cancer. You are in the front lines, all of you. You have a little bit different roles, but what you're doing is very, very important and I want to thank you for that.

We now adjourn the hearing.

[Whereupon, at 12 noon, the committee was adjourned, to reconvene at the call of the Chair.]

[Additional information submitted for the hearing record follows:]


Funding for the NCI Clinical Trials Cooperative Group Program, 1999-2003 Selected Groups and All Adult Groups
Total Adult Groups
Leukemia
Gynecologic Oncology
Breast and Bowel Cancer
87,017
105,021
113,887
121,278
115,000
24,000
22,000
20,000
18,000
16,000
14,000
12,000
10,000
Amount of Funding (Millions), Selected Groups
1999
2000
2001
2002
2003
Year
Prepared by the Committee on Government Reform, Minority Staff

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