



Division of Extramural Activities

Report of the National Cancer Institute Clinical Trials Program Review Group

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Executive Summary

Clinical research has always been an integral part of medical care: in many countries the two cannot be dissociated. Clinical Trials are the mechanism for the testing of new approaches to cancer prevention, diagnosis, and treatment. As such they are a critical component of the National Cancer Program and the National Cancer Institute's (NCI) research program. The NCI clinical trials program represents a unique opportunity to improve the survival and quality of life of patients with cancer, and to translate basic research into clinical application.

The clinical trials system is complex, involves many participants, and requires collaboration at all levels--between investigators and physicians, industry and academia, academia and NCI, and NCI and industry. In its entirety, the clinical trials system is an intricate and large research laboratory without walls. This complexity has bred inefficiencies and eroded the ability of the system to generate new ideas to reduce the cancer burden. Other challenges to clinical research, such as rapidly diminished opportunities for training, managed care, cost containment, low levels of participation in research, and diminishing levels of financial support for patient care and research have strained the system. The United States is now the world leader in both medical advances and in clinical treatment, in large part because of the excellence of clinical trials. Erosion of this structure will have a negative impact on our national health and economy over the long term.

At the same time several scientific and medical events have converged to force a reevaluation of the clinical trials system. Progress in cancer biology, genetics, immunology, imaging, and molecular biology has accelerated, creating new opportunities to pursue in clinical application. Opportunities offered through informatics and electronic communications offer an entirely new approach to communication and data transfer and analysis in the clinical research setting.

In April 1996 the Director of NCI and the Chair of the NCI Extramural Board of Scientific Advisors convened a group to review a series of issues affecting

the NCI clinical trials effort. This report is a response to that review. It addresses the question of how the cancer clinical trials system can respond to the exponential increase in new therapeutics and new technology in a changing fiscal and health care environment.

The clinical research community must find productive ways to respond to these challenges reducing the costs of research through efficiencies and by redefining study parameters, endpoints, and outcomes. In sum, the forces of expanding opportunities and contracting resources call for a new approach to setting priorities for, developing, and conducting clinical trials. In considering these challenges, the Review Group considered the following broad issues which form the structure of this report: recruiting and retention of clinical scientists; recruiting of participants to clinical trials; improving clinical trials methodology; increasing collaboration and cooperation in clinical trials; and the organizational framework and structure for implementation of clinical trials at NCI.

The Review Group made the following major recommendations regarding review, funding, design, oversight, and administration of the NCI clinical trials system. The recommendations are intended to create a more efficient and effective clinical research effort and to help NCI enhance and maintain a critical endeavor which is continually facing new internal and external challenges. Additional recommendations appear in the body of the report.

- A patient-oriented clinical cancer research and training study section in the NIH Division of Research Grants is critical.
- The NCI should increase funding for cooperative groups to fully recommended levels.
- In designing clinical trials, data collection should be reduced so that only data pertinent to the study endpoints and patient safety are accrued. In addition, NCI-funded efforts should include some large, uncomplicated trials in common cancers with minimal data requirements and accrual goals large enough to establish treatment differences definitively.
- Uniformity of data collection for patients on clinical trials in cooperative groups and cancer centers is essential.
- NCI should enlist the clinical trials and patient advocate communities as well as the pharmaceutical industry to work with the Food and Drug Administration to develop uniform standards and reporting requirements for everyone involved in oncology clinical trials (e.g., pharmaceutical industry, academia, cooperative groups, cancer centers).
- To be able to create and prioritize the best new ideas in cancer treatment and prevention, the NCI-funded cooperative groups and cancer centers should be provided with the means to access all relevant electronic databases, and should be primary participants in the

development and testing of the new NCI informatics system.

- For phase III and phase II studies not involving new agents, the Cancer Therapy Evaluation Program of the Division of Cancer Treatment, Diagnosis and Centers should approve study concepts and collaboratively establish research priorities, and its authority should be otherwise limited to regulatory and safety issues and prevention of unnecessary duplication.
- Representatives of patient and high-risk communities must be integrated into the clinical trials decision making process.
- Therapeutic trials conducted through the Community Clinical Oncology Program should be transferred to the Division of Cancer Treatment, Diagnosis and Centers. Cancer prevention studies conducted across the NCI clinical trials system should be the responsibility of a newly configured Division of Cancer Prevention and Control.
- To insure the continued success of cancer clinical trials, NCI should increase training opportunities for new and mid career investigators.
- NCI should develop strategies, including necessary databases, to convince payers that clinical trials are the preferred way to manage cancer patients, that they represent a better standard of care, and ultimately result in decreased costs.

The Review Group believes that if NCI considers and implements the recommendations outlined in this report, the overall structure and performance of the nation's clinical trials system will more efficiently and effectively explore new approaches to reducing the morbidity and mortality of cancer.

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Introduction

In November 1996 the National Cancer Institute announced that the cancer death rate in the United States fell by nearly 3 percent between 1991 and 1995, the first sustained decline since the national record keeping was instituted in the 1930s. Most of the overall drop in the death rate is due to declines in lung, colorectal, and prostate cancer deaths in men and breast, colorectal, and gynecologic cancer deaths in women. In addition, death rates from children's cancers have declined by more than 50 percent.

Efforts to reduce tobacco use are responsible for large reductions in cancer rates, particularly among men. Improvements in early diagnosis and screening have caught cancer at earlier and more treatable stages. Improved interventions, such as radiotherapy, chemotherapy, and surgery, have also contributed to reduced mortality. In addition to improvements in mortality rates for many malignancies, there have been important improvements in the quality of life for cancer survivors through less disfiguring and less damaging

surgical procedures, better pain control, and more effective medication for the side effects of cancer therapy.

These advances result from a 25-year program aimed at understanding the basic biology of the etiology and progression of cancer and then applying that knowledge to clinical practice and translating the observations of clinical research into explorations of the fundamental aspects of disease. Yet even taking into account this progress, overall cancer incidence continues to increase. By the year 2000, one person in three will develop cancer, which will account for 15 to 20 percent of total health care costs. Cancer remains a formidable enemy on many levels.

Ironically, the increase in cancer incidence simultaneously occurs with an explosion in knowledge about the molecular basis of cancer, which will lead us to better methods for prevention, diagnosis, and treatment. However, without the opportunity to apply this newfound knowledge to prevention of cancer in healthy individuals, and to the care of cancer patients, basic science will be caught in a logjam, unable to make its way to the bedside, and ultimately, to the reduction of the cancer burden.

Clinical research has always been an integral part of medical care: in many countries the two cannot be dissociated. The United States is now the world leader in both medical advances and in clinical treatment, in large part because of the excellence of clinical trials. Erosion of this structure will have a negative impact on our national economy over the long term.

Clinical research is a diverse and complex endeavor which, on the one hand, applies fundamental knowledge about disease processes to the development and testing of new diagnostic, prevention, and therapeutic advances, and on the other hand relies on clinical observations to pose research questions for the laboratory. Clinical trials are the mechanism for the testing of new approaches to cancer prevention, diagnosis, and treatment. As such they are a critical component of the National Cancer Program and the National Cancer Institute's (NCI) research program.

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The NCI Clinical Trials Structure

The NCI clinical trials program represents a unique opportunity to improve the survival and quality of life of patients with cancer, and to translate basic research into clinical application. The program also represents an effective model for cancer prevention trials among normal and high-risk populations, providing the opportunity to document biomarkers for further study.

NCI clinical trials are supported through a number of mechanisms, including the Divisions of Cancer Treatment, Diagnosis, and Centers Cancer Therapy

Evaluation Program (CTEP), which includes the Cooperative Groups Program and the Cancer Centers Program, and the Division of Cancer Prevention and Control through the Community Clinical Oncology Program (CCOP). Hundreds of clinical trials are supported through these and other research mechanisms, such as individual research grants, program project grants, cooperative agreements, and contracts. As such, the clinical trials system is complex, involves many participants, and requires collaboration at all levels-- between investigators and health care providers, industry and academia, academia and NCI, and NCI and industry. In its entirety, the clinical trials system is an intricate and large research laboratory without walls. It is difficult to quantify, describe, and evaluate. It is useful, however, to consider the system along NCI administrative lines.

The Cooperative Groups Program promotes and supports multi-center trials in cancer treatment, prevention, and early detection. More than 1,400 institutions and 8,500 investigators participate in Cooperative Group studies. Eleven NCI-sponsored cooperative groups annually place approximately 20,000 patients onto cancer treatment protocols, principally large randomized Phase III trials. The cooperative groups are funded by NCI but are administered extramurally through the cooperative agreement mechanism.

In addition, new anti-cancer agents are being studied in patients for the first time in Phase I and early Phase II clinical trials under NCI Investigational New Drug (IND) sponsorship in institutions funded by NCI cooperative agreements. Many of the 200 investigational agents and treatment strategies tested through this mechanism have been developed as a result of active NCI cooperation with industry and academic health centers and Cooperative Groups.

CCOP is an NCI mechanism that links community cancer specialists and primary care physicians with clinical cooperative groups and NCI-designated cancer centers to conduct cancer treatment, prevention, and control clinical trials. There are 52 CCOPs in 30 states, with 300 participating hospitals where approximately 3,000 physicians enter patients into trials. An additional 10 minority-based CCOPs are funded to enhance participation of minority populations in clinical trials research. Each year CCOPs enters more than 4,000 patients into cancer treatment and prevention clinical trials, accounting for about one-third of all patients on NCI Phase III treatment efficacy trials.

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Clinical Trials in a Changing Environment

This report addresses the question of whether the cancer clinical trials system can respond to the exponential increase in new therapeutics and new technology in a changing fiscal and health care environment. Several events have converged to force a reevaluation of the clinical trials system. Progress in

cancer biology, genetics, immunology, molecular biology and imaging technology have accelerated, creating new opportunities to pursue in clinical application. Opportunities offered through informatics and electronic communications offer an entirely new approach to communication and data transfer and analysis in the clinical research setting. At the same time, powerful forces to contain medical costs and limit NCI resources may prove to be rate-limiting factors in the application of new knowledge.

In recent years, health care organizations with an emphasis on price controls have changed the face of the practice of medicine, and by default, are influencing the conduct of clinical trials. Within this framework, the goal is to provide all patients with necessary services at the lowest possible cost. This trend in the delivery of health care poses several challenges to the clinical trials system, including access to patients and reimbursement for the costs of care for patients enrolled in clinical trials. The reluctance of some payers to put patients on clinical research studies reduces access by researchers to patient populations, the keystone of clinical research. Many fear that managed care discourages specialty care and limits opportunities to include research and research costs as part of patient care. In addition, patients are prevented from accessing new therapies. A number of additional economic forces challenge the clinical trials system in the United States, including reimbursement rules of the Health Care Financing Administration and the shift of industry toward international trials.

The clinical research community must find productive ways to respond to economic pressures by reducing the costs of research through efficiencies and by redefining study parameters, endpoints, and outcomes. In sum, the forces of expanding opportunities and contracting resources call for a new approach to setting priorities for, developing, and conducting clinical trials.

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Charge to the Review Group and Organization of the Report

The Clinical Trials Review Group was asked by the NCI Director and the Chair of the Extramural Board of Scientific Advisors to address the following questions in its review of the NCI clinical trials effort, as well as define additional issues as appropriate.

- Does the current configuration of the NCI Cooperative Group Program best serve the needs of the field? Is the present number, membership, organization, and trials portfolio of existing groups appropriate to take advantage of the most promising opportunities in therapy and diagnosis?
- How can the clinical trials program ensure that the most promising clinical research opportunities and the most important therapeutic questions are identified and engaged? In particular, how should the

program ensure that excellent insights, which are clinically applicable and are made in research laboratories, enter into the planning and action of cooperative trial groups?

- How might laboratory-to-clinic and clinic-to-laboratory information be enhanced in the clinical trials program?
- How should the program be organized to deal most effectively with the increasing pressures to route cancer patients away from academic medical centers?
- How can the work of the cooperative groups be organized so that the most important clinical research questions can be answered in the fastest possible time?
- What is the best system for ensuring optimal peer review of cooperative group efforts and trials?
- How can the extensive links between the pharmaceutical industry and the clinical trials program be optimized to ensure maximum productivity of the latter?
- What NCI funding mechanisms would provide the most research progress in the clinical trials program?
- What is the best way to organize the NCI administrative units which support and oversee the clinical trials program?
- What is the best relationship between the clinical trials program and other research programs of NCI, including those in prevention, early detection, diagnosis, and epidemiology/genetics?
- What options exist to ensure the continued training of clinical researchers?
- What are the incentives and disincentives for participating in clinical trials and how can NCI ensure that clinical trials are available to all segments of the population?

In considering these questions, the Review Group considered the following broad issues which form the structure of this report: retention and recruitment of clinical scientists; recruitment of participants to clinical trials; improving clinical trials methodology; increasing collaboration and cooperation in clinical trials; and the organizational framework and structure for implementation of clinical trials at NCI.

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Process of the Working Group

The Review Group met six times over an 11-month period between April 1996 and March 1997. It requested and received written and verbal reports from NCI staff, extramural scientists, representatives of scientific and medical organizations, administrators of academic health centers and managed care organizations, primary care physicians, advocacy groups, federal officials, and

representatives of industry. Meeting dates and acknowledgments appear in Appendix A.

This report is submitted to the Board of Scientific Counselors and the National Cancer Advisory Board for its consideration. The recommendations are aimed at improving the health of Americans through a productive and effective cancer clinical trials system. The recommendations attempt to address the sometimes competing interests of those invested in this complex enterprise, as difficult as that might be. The Review Group reminds those who will be responsible for implementing the recommendations, if accepted, that the enemy is cancer. The clinical trials system should assist innovation and creativity and make progress in the battle against this disease.

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Retention and Recruitment of Clinical Scientists in Oncology

Concerns about the need to more vigorously recruit and retain clinical researchers are not new and certainly have not been restricted to oncology. Clinical researchers, particularly in cancer, have been declared an "endangered species" since the 1970s. There have been numerous articles and committee reviews published in the past 15 years to address the personnel issue specifically, and more generally in the context of clinical research. The most recent attempt to review the status of clinical research and the training of clinical investigators is being conducted by the NIH Director's Panel on Clinical Research.¹ In 1995 a broad-based analysis of clinical research careers was undertaken by the Institute of Medicine². Personnel studies specific to oncology investigation also have been conducted.^{3,4} A 1994 analysis of the review of patient-oriented research applications by the NIH Division of Research Grants made several recommendations to improve the status of clinical investigators.⁵

The litany of recommendations ensuing from these reviews has become all too familiar to those concerned about the fate of the clinical scientist. These reports have repeatedly documented a continuing decrease in the number of young investigators entering academic careers in clinical research. They cite the prolonged training of clinical investigators, accumulated debt, the financial insecurity of embarking on an academic clinical research career, and the perceived slow academic advancement of role models in clinical research as key disincentives to pursuing a clinical research career.

Once trained, the apparent competitive disadvantage of clinical versus basic laboratory-based proposals in review is disheartening to anyone considering such a career. The number of RO1 applications for the development of new treatments for cancer patients is remarkably low, less than 4 percent of the total NCI RO1 pool of applications. This low rate of application is occurring either because there are not enough investigators prepared and trained to

submit high quality proposals or, more likely, that the RO1 system is not hospitable to clinical proposals. Once applications are submitted, they face the reality of lower scores and funding levels than their basic science counterparts.

The problems of recruiting and retaining talented individuals in clinical oncology, obtaining time and funding commitments for clinical research, writing high quality grant applications, and receiving appropriate peer review are not unique to clinical oncology. However, the Review Group found them to be more pressing because of the importance of translation of a backlog of research findings into clinical investigations, the unavailability of a wide array of effective standard therapies, and the intensity and duration of care required for cancer patients.

The findings of previous committees have led to series of recommendations to shore up both the training and continued research support for clinical investigators. There is little evidence that any of these recommendations have been acted on with much enthusiasm, although there have been modest efforts to expand training opportunities. Meanwhile, the status of the clinical researcher has worsened.

To ensure the success of the clinical trials system there must be a cadre of highly trained clinical investigators for several reasons: to discern the questions to be asked; to ensure that trials are conducted with the highest quality standards; and to ensure that there are trained clinical investigators in all oncologic specialties enrolling patients in trials. As basic science discoveries outstrip clinical capabilities to apply them, the void in clinical research will continue to increase. This can only be addressed by providing support for stable and rigorous academic training programs, recruiting physicians to become scientists or continue their professional development through mid career research training, and by ensuring that funds are available for clinical research proposals that seek to address significant problems in the diagnosis and treatment of cancer.

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Retention of Clinical Scientists Through Research Support

Existing peer review mechanisms mix clinical research proposals with basic laboratory studies, which has resulted in lower success rates for clinical protocols. Previous analyses of this phenomenon have concluded that the reviewers are frequently not clinical researchers and that clinical research proposals do poorly in competition against laboratory research proposals even when reviewed by appropriate peers.

Clinical scientists are expected to secure salary and other support through patient services. This takes time away from research and is an increasingly

tenuous way to raise funds. The pressures of managed care have exacerbated this situation as more emphasis is placed on the bottom line. In addition, there is no compensation for work done by clinical scientists in the community hospital setting. The clinician managing patients in the community setting provides a unique perspective to problems related to prevention, diagnosis and management. These individuals should be encouraged and retained to develop and manage protocols through the cooperative group process.

The relatively low success rate for clinical RO1 applications creates a vicious cycle for the clinical investigator. Within the academic medical setting, the ability to attract grant money plays a significant role in academic recognition and reward as well as in the distribution of suitable research space, resources, and personnel. The clinical investigator is then forced into a Catch 22 situation. In order to pay for research, he or she must generate patient revenues, which diminishes the amount of time and resources that can be spent on pursuing research. To compound this situation, the clinical requirements of accrediting and certification organizations minimize research opportunities.

It is vital to facilitate the development, submission, and approval of applications from clinical investigators to reverse this cycle. Clinical scientists need a period of stable support early in their career in order to become competitive in the R01 process. In addition, physician-scientists who refocus research efforts mid career in response to clinical needs should have available a funding mechanism which allows them to make that transition.

To create an environment in which clinical research applications can compete, the Review Group makes the following recommendations.

- **A patient-oriented clinical cancer research and training study section in the Division of Research Grants is critical for the success of oncology research.**
- **Awards to mid career and senior scientists should emphasize salary to ensure protected time for them to devote to clinical investigation.**

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Training for a Research Career

In the 1950s and 1960s NIH played a crucial role in the enormous growth of clinical research. Through its Clinical Center and its on-campus training programs, NIH produced a generation of superb physician scientists who then went on to careers in academic health centers around the nation. Training programs are now conducted primarily at academic health centers. It is not clear that these programs are adequate and flexible enough to meet the needs

of physicians who wish to pursue careers in clinical oncology in the era of managed care.

The Review Group recognizes clinical research to be a valid scientific discipline in its own right, which deserves training grant support, degree programs, tenure lines, and funding mechanisms. NCI is urged to formalize this recognition by supporting these training and career initiatives.

Physicians are likely to choose research careers at various points during their training: prior to or on entering medical school; during medical school; or later, during house staff officer training or during a clinical fellowship. Training for physicians to conduct clinical research has evolved from traditional postdoctoral fellowships to more formal programs that incorporate course work in areas such as molecular biology, genetics, and cellular physiology. There are similar programs for Ph.D. scientists in human biology and clinical investigation. In general, there is agreement that these institutional training programs are effective and should be continued. But there are too few institutions that have all the essential elements to develop high quality training programs in clinical oncology research.

The Review Group considers the Johns Hopkins Graduate Training program to be a model program in that it meets the need for education in research methodologies and provides for mentored clinical research and an opportunity for original clinical investigation. In addition, the Institutional Training Grant (T32) mechanism of NIH has been a viable means for training the physician scientist although the duration of support might be too short for the clinician.

The NIH mechanisms for postdoctoral training for physicians have traditionally occurred through the K series awards, which require a varying amount of research experience. These awards, specifically the KO8 and K12 awards, provide a protected period of research training for clinical investigators. In addition, the NCI-designated cancer centers are potentially optimal environments for establishing the early research careers of physician scientists. It is not clear that this funding mechanism has been exploited to its fullest extent.

To increase the training opportunities for new and K.O. investigators the Review Group makes the following recommendations.

- **Clinical investigator salary lines should be made available on cancer center's core grants. These salary lines should be for a three to five-year duration.**
- **K12 and T32 awards should be expanded and K08 awards should be directed to patient-oriented research. NCI should create new awards for junior faculty and for K.O. salary support.**
- **The NCI should fund at least 10 fellowship programs (similar to**

**the Johns Hopkins University Institutional Training Program)
which provide a formalized academic degree program for clinical
scientists.**

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Recruitment of Participants in Clinical Trials

Clinical, or patient-oriented research, is the bridge between laboratory discoveries and improvements in cancer therapies. This bridge is bidirectional: it carries knowledge from basic science into clinical use and transmits scientific questions developed from physicians' observations into laboratory investigation.

Without clinical research, recent discoveries in molecular genetics will not be translated into effective interventions for people with cancer, new chemotherapeutics cannot be safely offered to patient populations, and new prevention strategies cannot be tested for their ability to lower cancer incidence. Without carefully designed research in humans we cannot know at what point we have the necessary laboratory knowledge to stop cancer before it starts, slow its progression, or reverse its negative consequences.

An effective national cancer program can never be implemented without patient-oriented research. This requires that individuals be willing, able, and available to participate in clinical trials. Participation in clinical trials is an opportunity not only for discovery, but also to experience the most promising and valuable new preventions, diagnoses, screening procedures, and therapies.

Despite the potential therapeutic advantage of participating in clinical trials, the current number of eligible cancer patients entering clinical research studies is less than 3 percent. This is related primarily to the impediments to enrollment into cancer clinical trials as well as the limited funding of cooperative groups, which is the critical rate-limiting barrier to increased accrual. And even in studies where accrual is good, compliance and retention are not optimal. As a result, slow accrual and retention rates give way to delayed completion of clinical trials, resulting in cost inefficiencies, slowed translation of bench science, and potentially inequitable distribution of the risks and benefits of research.

There are many reasons why eligible individuals are not being enrolled in clinical trials: they are unaware that such an opportunity exists; they are alienated from the usual health care channels which provide access to trials; the trial is too complex and informed consent cannot be obtained; their primary care physician is unaware or unwilling to seek out relevant trials on behalf of his or her patients; trials are overly exclusive; or there are institutional obstacles to recruitment, primarily cost. From the perspective of

the investigator, patient accrual might be limited strictly by money, that is, there are simply not enough funds available to recruit the necessary number of individuals to make a trial effective and useful.

The Recruitment Process - Barriers for the Physician

Identifying and enrolling suitable individuals in clinical trials is often arduous and time consuming. Considerable effort is expended by the enrolling physician collecting baseline data and screening individuals for enrollment. Data requirements of CTEP, the cooperative groups, the NIH Office for Protection from Research Risks, and the Food and Drug Administration are not uniform and are sometimes irrelevant to a study.

It is the belief of the Review Group that there are far too many data requirements as well as too many exclusion criteria in the current clinical trials system. Potential enrollees are disqualified for seemingly arbitrary reasons from trials for which they would otherwise qualify. In addition, forms required for trial randomization do not take advantage of computer systems creating even more work for the investigator. The resulting enrollment system is slow, inefficient and costly. The money that could be saved through a more uniform and streamlined process could be used to enroll more patients in trials.

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Payment for Patient Care

The managed care system is designed to limit costs by limiting discussions of therapeutic options, limiting expensive diagnostic tests, and limiting special referrals, such as to oncologists. There are financial incentives to the "gatekeeper" physicians who apply these principles. Managed care organizations are often unwilling to pay for even the patient care costs associated with clinical trials. In addition, clinical trials are poorly and inconsistently covered by Medicaid and Medicare health maintenance organizations, despite evidence that patients on trials receive good, often superior, medical care.

Lack of third-party reimbursement for clinical trials may be one of the most critical barriers to patient participation. Cancer screening and other ancillary tests or services are available to most managed care patients, but are often not covered. Aside from the conduct of clinical trials, physicians might encounter problems recovering costs, making referrals, and requesting outpatient services.

Payers have the potential to provide improvements in wellness services, protect patients from ineffective or dangerous cancer treatments, enroll subscribers in prevention and control studies, and establish standards for cost-effectiveness. The Review Group believes that insurers and health care

organizations can offer quality cancer care to their subscribers while assisting well-designed studies that will identify cost-effective therapies and technologies. All efforts should be made to ensure reimbursement of patient costs for cancer clinical trials that are of therapeutic intent and have been approved by NCI or the Food and Drug Administration as well as an Institutional Review Board.

The recent establishment of an interagency agreement between NCI and the Department of Defense, to provide coverage for DOD's managed care beneficiaries who enroll in NCI-sponsored clinical trials, is a milestone. The subsequent agreement between NCI and the Department of Veterans Affairs to provide access for veterans to NCI trials also serves as a model for ensuring that beneficiaries of the largest payer/provider organizations in the country have access to cancer clinical trials.

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Public Education and Community Involvement

To be successful, recruitment approaches must be tailored to the culture and needs of each community and must be well publicized. It is essential that patients and communities at risk be represented at all levels of the trials system, from development through implementation. Patient advocacy groups provide invaluable insight into the needs of the patient and can be useful in trial design and review, recruitment, access, development of informed consent processes, monitoring, and dissemination of research results. Once an individual is enrolled in a trial, patient support groups can greatly improve compliance and retention.

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Working with Community Physicians

Education in the community through health care providers and direct marketing campaigns can improve accrual. Programs that actively engage all types of community physicians in the trial process are likely to make the difference between a successful and unsuccessful trial. Previous studies have shown that community physicians feel that trials are inconvenient for patients; place a financial burden on them; and put at risk the physician's relationship with the patient. Physicians do not want to abandon patients they have been working with for many years. One of the primary drawbacks to physician enrollment practices is the extra time required, the amount of paperwork, the complexity of modern trials, and the difficulty of explaining randomization.

Physician networks are a valuable way of recruiting patients into trials while allowing them to continue to be seen by their primary physician. The cooperative group outreach program (CGOP) and CCOPs are additional mechanisms for primary care physicians to maintain contact with patients who

join clinical trials. NCI-designated cancer centers are an additional, but insufficiently tapped, source for accrual. Participation of cancer centers, which have a community focus in their treatment efforts, would not only add patients to trials but also would enhance the quality of the study. In addition, cooperation of cancer centers in the clinical trials of cooperative groups does not appear to be rewarded or encouraged when the center undergoes NCI review.

There is a need to promote cancer research within the medical community. Many critical decisions regarding treatment and accrual to trials are made locally by physicians, hospitals, managed care systems, and local and state governments

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Informed Consent

The informed consent process is a broad issue reaching far beyond the purview of this Review Group. It is a topic which engenders much debate among scientists who must obtain consent and individuals who must provide it. Clearly, the process of recruiting individuals into clinical trials must be done with sensitivity. Investigators must avoid inducements and coercion, and be aware of cultural and socioeconomic factors which might influence an individual's decision to enter and stay in a trial. However, it is the opinion of the Review Group that the informed consent process is onerous and overly cautious. In many cases it has become a disclaimer for institutions rather than information for the participant. As a result, true informed consent is not being obtained and the informed process itself may be inappropriately deterring individuals from participating in clinical trials. An enhanced and improved informed consent education process for both patients and physicians might alleviate some of these difficulties.

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Participation of Minorities and Underserved Populations

The Director of NCI has written that there is an urgent need to ensure adequate, equitable, full, and meaningful participation by minority populations in clinical research.⁶ Achieving equity in terms of distribution related to cancer incidence of the population is crucial for scientific, medical, and ethical reasons. It is essential to collect data on different subpopulations for differences in outcomes, natural history, responses, and other areas, and to recognize and adapt to the special cultural and social issues relevant to minority and underserved populations. It is known that the cancer burden varies across subpopulations and that some of the highest cancer rates are found in minority populations, although tremendous gains have been made in reducing cancer mortality among African Americans. Designing interventions that are translatable across many subpopulations should be an important goal

of clinical oncology research.

Despite recent gains in cancer survival among minority populations, challenges remain in enrolling minority populations in ongoing clinical research, including: lack of access to a health care system likely to recruit patients into trials or cover costs; discomfort between community physicians and their patients about the trials process; and distrust of the medical establishment. Some of these challenges are enormous and beyond the capacity of NCI's ability to affect change. Nevertheless, efforts are being made by NCI to improve the process.

In addition to the NIH-wide requirements to ensure that clinical research consider the variables of gender, ethnic, racial, and socioeconomic variables, NCI has initiated several new efforts to increase minority participation in all aspects of clinical research. These include: a Request for Applications (RFA) that invites investigator-initiated RO1 grant applications for research to develop, implement, and test well-defined, hypothesis-based interventions in cancer prevention and screening clinical trials; an RFA that solicits R03 grants applications for pilot studies to test new ideas and gather information that will lead to the development of effective models and strategies to improve the participation of women and minority groups as participants in trials; and an RFA to encourage newly trained clinicians to acquire clinical training and expertise in clinical oncology and to increase the representation of minorities in clinical oncology. In addition, the Minority-Based Community Clinical Oncology Program (MBCCOP) has demonstrated some success in minority recruitment into treatment trials.

The Review Group applauds NCI's efforts in this area and encourages the continued attention to and encouragement of participation of minority and underserved populations in NCI-supported clinical research.

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Recommendations

To remove some of the barriers to participation in clinical trials and to ease the enrollment process, the Review Group makes the following recommendations.

- The NCI should continue to improve its efforts to recruit and retain minorities, underserved populations and the elderly in clinical trials and to tailor its approaches to address linguistic and cultural differences.
- The NCI should increase funding to cooperative groups to fully recommended levels to ensure adequate patient accrual.
- In designing clinical trials, data collection should be reduced so that only data pertinent to the study endpoints and patient safety are

accrued. In addition, NCI-funded efforts should include some large, uncomplicated trials in common cancers with minimal data requirements and accrual goals large enough to establish treatment differences definitively.

- Entry criteria for all studies need to be simplified and broadened. A range, rather than an absolute set, of parameters should be considered.
- The NCI-designated cancer centers should be encouraged to participate in cooperative group research. In addition, participation in cooperative group studies should be viewed favorably in the cancer center review process.
- The NCI should continue to develop strategies (including necessary data bases) to convince payers that clinical trials are the preferred way to manage patients, that they represent a better standard of care, and ultimately result in decreased costs.
- High quality patient-oriented public awareness campaigns presenting the value of clinical trials should be a high priority.
- Representatives of the patient and high-risk communities need to be integrated into the clinical trials decision making process.
- The informed consent process must be greatly modified and simplified. The NCI should work with OPRR to develop a template for informed consent for distribution to clinical scientists and the patient community

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Improving Efficiency in Clinical Trial Methodology

The clinical trials methodologies used by the 11 cooperative groups and 51 cancer centers have created a system described as a "Tower of Babel" by some members of the Review Group, in which protocol format, clinical endpoints, data collection forms, informed consent, toxicity criteria, and computerization of data differ among groups. Acceptable endpoints for studies must be reconsidered, as should eligibility criteria, toxicity criteria, and biostatistical criteria. To advance the clinical trials system, NCI must consider it mandatory to seek uniformity among groups for reasons of efficiency and comparability. Such uniformity should not impair a group's ability to retain intellectual property interests.

The Review Group discussed a variety of approaches to make the clinical trials system more efficient and effective by changing the way trials are conducted. They included improvements in the methodology used in data collection in clinical trials, improvements in intergroup studies, and better electronic transfer of data among groups.

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Uniformity in Data Collection Methods

There are a number of ways in which methodology can be harmonized among groups conducting clinical trials:

- Uniformity in data collection for clinical trials is essential.
- All groups and cancer centers should **use the same protocol guidelines** so that each critical element in a format is the same across protocols. This will allow clinical research associates, who deal with the protocols on a daily basis, to move easily and efficiently from protocol to protocol, regardless of the group of origin.
- The eligibility criteria for all cancer clinical trials should be simplified in order to require minimal input at the time of registration of individuals, and to substantially reduce the workload for the individual conducting the registration.
- **Study endpoints should be standardized.** Common endpoints would render protocols simpler and more uniform. This could result in substantial cost savings by reducing the number of study parameters necessary to document surrogate endpoints, such as partial and complete response to treatment.
- To limit the cost of clinical trials, NCI and groups conducting trials should **reduce the number of study parameters required** in any given trial to only those that bear on patient safety and documentation of endpoints.
- **Rapid protocol development is critical to the ability to implement new ideas and concepts in an expeditious fashion.** Groups should develop a common algorithm for protocol development in order to minimize the time necessary to develop and obtain a letter of intent or concept to NCI for consideration and review.
- **All cooperative groups and cancer centers should use the same common data collection forms.** This would optimize the ability to exchange data in intergroup studies. Flow sheet information should be captured on single patient encounter forms to allow for computerization of data which could then be sent electronically to the appropriate statistical center.
- **Common toxicity criteria should be developed** in order to overcome the complexity of toxicity tables that now exist. This would allow for uniform toxicity criteria across all studies and would provide comparability across the system.
- **Common biostatistical principles should be developed** for use in evaluating data such as endpoints and sample size. There is considerable variation in statistical sections from one group to another concerning such issues as sample size, design considerations such as stratification, early stopping rules, and handling subset analyses.
- **Common and simplified adverse drug reaction and adverse event reaction reporting is essential to creating a system that protects**

clinical trial participants.

- **Simplified informed consent documents** will assist both trial participants and physicians (see also section III) and are essential.

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Improvement of Intergroup Studies and the Size of the Cooperative Group Enterprise

Intergroup studies are an important means to avoiding redundancy among cooperative groups and for meeting large sample size accrual goals, but they need to be improved through streamlining of operations and enhancement of scientific quality. One of the reasons intergroup trials are expensive is because patients are registered by multiple groups. Even though managed by one group, each of the groups process the required paperwork, conduct follow up, and even store tissues. This duplication is largely a result of the perceived need for each group to monitor accrual and data quality for its own members. This duplication of effort becomes even more problematic because the group data collection systems are often incompatible. Information collected on investigators, institutional review board reviews, and registration privileges, for example, are not uniform. Specimen tracking and data sharing are not efficient and sometimes ineffective.

Intergroup trials also become an ordeal because they overload the statistical centers: large intergroup studies tend to be adjuvant studies requiring many years of follow up. Managing high volumes and multiple groups is difficult for all groups involved as well as non-group collaborators. Complicated studies or studies with extensive data submission requirements overwhelm the system.

The protocol development processes for intergroup trials consist of tediously long rounds of discussions at intergroup meetings, intragroup meetings, negotiations with CTEP, conference calls, and mailings. The resulting study designs are frequently compromises which are unacceptable to the one or more groups. Disease committee chairs often feel they have lost control of their own committees and that politics, rather than scientific excellence, predominate in the protocol development process.

If the cooperative groups are not large enough to conduct a trial expeditiously, then it might seem reasonable to create fewer, larger groups, rather than pay more per patient through intergroup studies. The high cost per patient of intergroup studies means less funds are available to accrue patients. The number of groups in existence creates a system where there is unnecessary duplication of efforts. The Review Group recognized that considerable controversy surrounds the issue of the number of cooperative groups and believed it was too conflicted to make recommendations about whether and

how to reduce the number. It recognized that fewer groups with higher levels of funding per group would actually increase patient accrual while lowering costs. However, the review Group makes several recommendations regarding streamlining and centralization of group efforts as a means to addressing issues of redundancy. After attempts to remove inefficiencies have been addressed, it would seem prudent for the NCI Director to carefully scrutinize whether the number of cooperative groups is justified. As indicated on page 25, a small committee of individuals without vested interests in any of the cooperative groups could make recommendations to the Director on this issue.

To improve the intergroup study process and to meet the goal of cost-effectiveness in the clinical trials system, the Review Group makes the following recommendations:

- **The decision to conduct an intergroup trial should be based on investigator initiative. When conducted, intergroup trials should be harmonized and simplified.**
- **When intergroup studies are judged necessary, extra funds should be provided by NCI to the coordinating group to cover additional expenses.** This is particularly critical during registration and evaluation, but also is needed for patients in follow up.
- **All groups participating in an intergroup study should be able to conduct direct registration and submit forms directly to the coordinating group.**
- **Systems for awarding proper credit and funding to each institution participating in an intergroup study must be developed.**
- **Tissue samples and related clinical data should be stored and maintained**

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Enhanced Communications

If the recommendations listed above pertaining to standardization and harmonization of data collection are implemented, electronic transfer of communication could occur among groups, non-group trials, cancer centers, and NCI. A relatively inexpensive format could be developed for computerized data entry at the point of service. Institutions without the required computing capabilities could forward data to the appropriate statistical center. These considerations led the Review Group to recommend the following:

- **To be able to create and prioritize the best new ideas in cancer treatment and prevention, the NCI-funded cooperative groups and cancer centers should be provided with the means to access all relevant electronic databases, and should be primary participants**

in development and testing of the new NCI informatics system. A single informatics system for the NCI, all cancer centers, and all cooperative groups is important to the success of the clinical trials program.

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Increasing Collaboration and Cooperation in Clinical Trials

The National Cancer Institute (NCI) has an established clinical trials mechanism that emphasizes disease-oriented studies. NCI trials have a tremendous impact on standard of care, which has a major impact on the way oncology is practiced in the United States. However, the process of moving basic laboratory discoveries to accepted and proven therapies for cancer patients is a long, arduous, and expensive process. To improve the quality of the cancer clinical trials system in the United States this process must be more efficient, expanded in scope, and of highest priority for all involved. There are several key players in the clinical trial process including the scientific community, primary care providers and their patients, NCI through its various funding mechanisms, the NIH Office for Protection from Research Risks, Institutional Review Boards, industry, and the Food and Drug Administration (FDA). Without collaboration among and cooperation of all these parties, the trials system will become inefficient, unresponsive, and unduly expensive.

An important area of collaboration is between clinical and laboratory scientists to encourage "translational" research. Facilitating this communication and collaboration is a major focus in cancer centers. It is also important in insuring that the highest quality and most innovative studies are performed in the cooperative group setting. These interactions should be encouraged as an important area for cooperative group action.

The Review Group considered several issues which require the cooperation of groups beyond NCI and recognizes that, as a result, recommendations are limited in that they can only apply to NCI and its legislative and administrative mandate. Nevertheless, there are a number of actions which NCI can pursue to improve the efficiency and effectiveness of its working relationships with the FDA, the NCI cooperative groups, and those who pay for the costs of patient care in clinical trials.

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Food and Drug Administration - NCI Interactions

In response to many years of complaint and resultant legislative action, the FDA has made progress in expediting the clinical drug development and approval process, particularly for new therapies in life-threatening and severely debilitating illnesses. The time line for FDA action on Investigational

New Drugs (INDs) is 30 days. For New Drug Application (NDA) submissions following Phase II trials the FDA must decide if a submission is reviewable within 60 days. Complete action for standard drugs is required within 12 months and within six months for priority drugs.

In testimony provided to the Review Group, the FDA reported that it continues to find ways to expedite the review of clinical cancer research through early and frequent contacts with sponsors, increased collaboration with NCI and its cooperative groups, provision of initial marketing approvals based on the limited evidence of effectiveness and safety; and provision of marketing exclusivity for innovators.

The FDA also indicated that it intends to provide additional guidelines about preclinical and clinical data requirements, an issue of interest to the Review Group because of the perception that FDA data requirements do not address the specific aspects of oncology drugs. Although anticancer drugs are eventually channeled to the Oncology Drugs Advisory Committee (ODAC) there has been inconsistent review of these agents across the various FDA committees with jurisdiction (e.g., metabolic and endocrine products, hormonal agents, and radiotherapeutic agents). Disparities exist in requirements for interim analyses and decision points, including the acceptance of objective responses, and the willingness to review early results and small numbers of patients.

The data requirements for NCI often are different from those for the FDA. In addition, the confidentiality of data required by industry cannot always be protected with assurance in NCI clinical trials. The competing demands of the public's right to know versus industry's desire to protect proprietary data have not been adequately resolved, resulting in sometimes poor relationships between NCI and private interests.

The Division of Oncology Drug Products reports increased levels of activity in clinical cancer drug development in recent years. Despite this increase, only about one in ten INDs results in NDAs. According to the FDA many of the drugs in the pipeline are of marginal value, with modest efficacy, and significant toxicities. Applications for breakthrough drugs, however, receive expedited review and there is hope that new cancer drug development processes at NCI and at major academic institutions will improve the number and quality of drugs approved in the next ten years. This promise is premised on increased and improved communication among NCI, the cooperative groups, and industry. As new drugs are developed, it might be necessary to revise the surrogate or final endpoints required for data collection. This requires formal and ongoing communication among the scientific and regulatory communities.

NCI-Industry-Cooperative Group Interactions

Representatives of drug companies testified to the Review Group that the speed with which academic medical centers and clinical cooperative groups approach clinical research contrasts unfavorably with the faster approach of contract research organizations, or CROs. Academic institutions and cooperative groups are slower to review and implement trials and do not often share the urgency or sense of ownership of private interests.

Legal and contracting issues at universities, delays in negotiating Cooperative Research and Development Agreements, and disputes about intellectual property and termination clauses cost both time and money, although there have been exceptional cases where collaboration has been expeditious and mutually agreeable.

Finally, changing referral patterns are creating difficulties for universities and cancer centers in attracting patients to clinical trials. Cost shifting to the trial sponsor is resulting in a higher average cost per patient in the United States compared with international trials. In some cases, the full cost of patient care is passed to the sponsor, including standard care that was formerly paid by the insurance of health care carriers. If the clinical trials system is to remain a public, as well as private, endeavor, NCI, the cooperative groups, and the academic health centers need to resolve several issues including the time it takes to begin a trial, standardization of protocols for purposes of streamlining, payment for standard care, and institutional overhead--all issues which are prolonging the approval, initiation, and conduct of trials.

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Modifying Operations to Facilitate Collaboration

To make collaboration with NCI and NCI cooperative groups a more attractive option for industry and managed care organizations, several measures must be taken to improve the efficiency, speed, and accountability of the planning, implementation, and review of clinical trials. In order to advance treatment modalities or preventive measures to the point where they can be commercialized, the clinical trials process must be streamlined.

The Decision Network: The Decision Network is an internal multi disciplinary committee of NCI scientists who routinely make decisions about preclinical drug development activities. The committee screens agents for acquisition, makes decisions regarding commitment of contract resources to develop an acceptable formulation, determine the optimal dose, route, and schedule for further toxicologic studies, procure sufficient amounts of the material for further preclinical studies, and determine the schedule for demonstration of antitumor activity and feasibility of animal testing. The Decision Network helps to bridge the gap between RO1-supported preclinical work and the

first clinical step toward IND submission. It is the only public "laboratory" that can focus on unpatentable, orphan drugs, and on second indications for which companies have no interest in funding. It is the opinion of the Review Group that the Decision Network serves a valuable service but is underutilized due to lack of advertising on the part of NCI.

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Cooperative Groups: Cooperative groups function to eradicate cancer, not to survive as organizational entities. Cooperative group chairs, in addition to their clinical and academic responsibilities, are responsible for raising sufficient funds and overseeing the conduct of meaningful clinical trials. In an environment of constrained resources and a highly complex clinical trials bureaucracy, these individuals spend a significant amount of time meeting these goals. They are unlikely to receive financial support or recognition from their parent institution for completion of these responsibilities. Because the cooperative group mechanism does not always provide salary support for cooperative group chairs, academic institutions are likely to devalue the important role these individuals play. The cooperative group chairs are the central figures in facilitating collaboration in specific trials.

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Sharing the Cost of Clinical Trials

Clinical research is a costly undertaking, as is training the next generation of health care practitioners and clinical scientists. Much of the additional money derived from clinical practice in the fee-for-service setting is not available under managed care. The dollars that were formerly available to support pilot research, trainees, and junior faculty, and to offset the higher cost of patient care in research settings are no longer obtainable.

The costs of clinical research and training increasingly are becoming a troublesome issue for academic medical centers which have financed clinical research through a complex system of cross-subsidization. Research funds are drawn from Medicare, patient revenues, grants, private industry, and tuition. With more Medicare patients being channeled into managed care organizations and away from academic health centers, the Medicare revenues once used to finance research are rapidly diminishing. If clinical research capacity in the academic setting is lost, some fear, there will be an immediate and direct influence on the volume and types of clinical trials that will be conducted. Innovative, long-term, and potentially high risk trials of new drugs, investigations of new applications for existing products, and the development of drugs for the so-called "orphan diseases" could be without a home. In addition, coverage for standard care for patients enrolled in clinical trials is sometimes denied by payers.

The nature and extent of the impact of managed care on clinical research is currently unclear. Some observers see the search for cost savings as incompatible with clinical research. Others view cost savings as an important result of clinical research. Clearly, there is room for clinical research in the managed care setting. The Review Group heard testimony regarding premarketing drug studies conducted by nonprofit managed care organizations. However, if the clinical trials system is to survive in the managed care environment, greater effort must be made to determine the actual costs of trials with the ultimate goal of finding ways to cut costs without hindering quality. The NCI could encourage the Health Care Financing Administration (HCFA) to take a lead role in assessing costs of clinical trials and demonstrating that clinical trials are the preferred way of managing patients.

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Interactions with the Office for Protection from Research Risks (OPRR)

In response to the inconsistency and potential inequities in the quality of Institutional Review Boards (IRBs) across the United States, NCI must take a proactive role in the development of quality assurance and training programs for IRBs and investigators. It may also be necessary to establish a more streamlined IRB process (either regionally or nationally) for multi-center, cooperative group or intergroup trials to assure that all patients are treated equally, and are provided the opportunity to participate in research in institutions close to their home.

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Recommendations

- **The NCI should urge the FDA to form a single oncology advisory committee with provision for obtaining necessary expertise for ad hoc review.**
- **The NCI should enlist the clinical trials and patient communities as well as the pharmaceutical industry to work with the FDA to develop uniform standards and reporting requirements for everyone involved in oncology clinical trials (e.g., pharmaceutical industry, academia, cooperative groups).**
- **The NCI should appoint a group to develop legal templates for interactions between universities, cooperative groups, and industry for material transfer agreements, clinical cooperative agreements, and Cooperative Research And Development Agreements (CRADAs).**
- **The public should have access to all information about ongoing clinical trials (e.g., through PDQ). The only justified situations for undisclosed trials are those which are funded, in total, by private interests.**

- **The cooperative group grants should include a salary commitment to the responsible committee chairs to ensure that time and effort is matched by salary support in the planning, implementation, and review of trials.**
- **The cooperative groups and CTEP need well-defined time lines for protocol development, approval, and activation with clearly stated positive and negative consequences of not meeting those time lines.**
- **The Decision Network needs to be publicized and would benefit from external input. CTEP must clarify its role in reviewing novel drugs with questionable patent status to better move these agents toward clinical trials.**
- **The NCI should work with other governmental agencies and private organizations, including third party payers, to determine the actual costs associated with Phase I through IV clinical trials, and should develop a plan for funding the research required to determine these costs.**

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NCI Administrative Structure and the Clinical Trials System

NCI extramural clinical trials are not coordinated by a single organizational unit. However, the largest clinical trials activity is sponsored by the Cancer Therapy Evaluation Program (CTEP) of the Division of Cancer Treatment, Diagnosis, and Centers (DCTDC). Among CTEP's responsibilities are the administration and coordination of the NCI-sponsored Clinical Trials Cooperative Groups, Phase I and Phase II new agent development contracts, and RO1 and PO1 grants programs. The Community Clinical Oncology Program (CCOP) activity of the Cooperative Groups is administered through the Community Oncology Program of the Division of Cancer Prevention and Control (DCPC).

New agent development for treatment applications is conducted principally through the Investigational Drug Branch of CTEP. Regulatory activities for CTEP are provided by the Regulatory Affairs Branch. Prioritization for new treatment development is conducted through the Decision Network of DCTDC, which stages an agent from acquisition screening through filing of an Investigational New Drug Application. The Clinical Trials Monitoring Branch of CTEP supervises all treatment-related quality assurance and auditing activities, including those conducted by cooperative groups, cancer centers, and involving NCI-sponsored investigational agents.

The nationwide Cooperative Groups Program promotes and supports clinical trials in cancer treatment, prevention, and early detection. The essential feature of the Cooperative Groups Program is the support of organizations that continually generate and conduct new clinical trials. More than 1,400

institutions and 8,500 investigators participate in cooperative group studies. Eleven cooperative groups annually place about 20,000 new patients onto cancer treatment protocols, principally large randomized Phase III clinical trials which have been responsible for establishing the current state of the art for cancer treatment. In addition, agents being studied for the first time in patients are entered into Phase I and Phase II clinical trials, many conducted under NCI Investigational New Drug sponsorship in institutions funded by NCI cooperative agreements.

As noted on page 18, it may be that a smaller number of cooperative study groups would be appropriate. However, our experience would suggest that this will only be achieved by the identification of a special, small committee made up of individuals who have no vested interest in the existing groups and with the charge of reviewing numbers and performance of existing groups and making a recommendation about optimal number. These recommendations should be based on issues of quality not process. Any mechanism of review of cooperative groups needs to emphasize the goals and values desired in the clinical trials program.

The NCI budget for the Cooperative Groups Program was nearly \$90 million in 1997. Since the early 1980s, cooperative groups have been supported through a cooperative agreement, rather than a more traditional investigator-initiated grant mechanism. The cooperative agreement mechanism stipulates that the group and NCI share the responsibility for ensuring that the best and most important clinical research is conducted within the limits of available research support and patient populations.

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Reforming the Cancer Therapy Evaluation Program

It is the belief of the Review Group that the conversion of the cooperative group funding mechanism to the cooperative agreement in the early 1980s signaled a significant transition in the relationship between NCI and the cooperative groups. It was at this point that NCI took a more active role in the direction of group research. To its credit, CTEP has provided an important service as a central clearing house for clinical trials concepts and letters of intent.

The protocol review process of CTEP, which serves as an extension of its role as a clearinghouse for clinical trials, is an excellent service for the cooperative groups. However, the process has become cumbersome, overly administrative, and slow. It takes too long for the groups and CTEP to activate large trials, particularly if they are phase III trials involving more than one group. The prolonged period from initiation to activation has the effect of weakening the protocol as it goes through multiple iterations and may result in a trial conducted too late to answer critical questions about an agent before it is

placed in use. It is the opinion of the Review Group that CTEP's involvement in the trial development and activation process should be reduced in phase III trials and phase II trials not involving new agents. Phase I studies and others involving new agents will continue to require more active CTEP involvement.

An additional area of concern regarding CTEP is the process by which Cooperative Research and Development Agreements (CRADAs) are formed. Through this mechanism CTEP staff and a pharmaceutical interest agree on an NCI-directed development plan for new compounds. This process ultimately obligates cooperative groups in many complex ways to conform with the language of the CRADA. The CRADA negotiations are conducted confidentially, for reasons of intellectual property protection, but without the input of the cooperative groups, which are then asked to conduct the trials on behalf of CTEP. This practice has created hard feeling and misunderstandings and should be reevaluated.

The Review Group strongly believes that the authority for prioritization of clinical trials should be established and retained with the cooperative groups. The role of NCI in this process should be redefined, including the terms of the cooperative group agreements. The recommended changes in the agreements should depend on the nature of the clinical trial. To provide more financial and operational stability, and in exchange for the additional burden imposed by the review process the award period for the cooperative groups should be increased.

The Review Group recommends the following specific actions with respect to CTEP.

- **For phase III and phase II studies not involving new agents CTEP is to approve study concepts and collaboratively establish research priorities, and its authority should be otherwise limited to regulatory and safety issues and prevention of unnecessary duplication.**
- **For studies involving investigational new agents, CTEP should retain its current legislated authority and responsibility, in partnership with industry and the cooperative groups.**
- **For most prevention and control studies, the cooperative groups should be provided with the authority to establish priorities and conduct studies. For large-scale cancer prevention and controlled phase III studies, DCPC (or, preferably, a combined DCTDC/DCPC review process) should actively participate in concept approval and priority setting.**
- **Amendments and addenda to the trials should become the full responsibility of the group conducting the study rather than the ultimate control residing within NCI. Amendments should be filed with, but not require the approval of, NCI.**

- The separate protocol review processes of DCTDC and DCPC should be combined to avoid the delays, contradictions, and perplexity of the existing mechanism.
- Given the fact that the current cooperative groups are 17 to 41 years old and each has successfully completed multiple competitive renewal applications, if legislatively possible, the interval for funding established cooperative groups should be lengthened from the current five years to eight to 10 years. New groups, for which there is no previous track record, should be limited to the current interval and be granted longer funding durations after successfully completing two competitive renewal applications.
- Cooperative groups should be engaged as early as possible in CTEP CRADA negotiations that will require group participation.

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Clinical Trials and the Community Clinical Oncology Program

All of the large multi disciplinary cooperative groups pursue the aims of NCI in bringing the advantages of state-of-the-art cancer treatment, prevention and control research to individuals in their own communities through participation as a research base in the CCOP program. It is the impression of the Review Group that much of the clinical research currently conducted by CCOP is primarily therapeutic and should be administered by the Division of Cancer Treatment, Diagnosis and Centers.

In providing a research base to CCOP, cooperative groups develop protocols, conduct data management and analysis, and provide quality assurance. Approximately 30 percent of accrual to cooperative group treatment trials occurs in CCOPs. However, the shrinking credit value (\$350/credit)--which has not changed since CCOP's inception--has created severe financial difficulties for the cooperative groups.

Unfunded NCI mandates and exponentially increasing indirect cost rates, salaries, and supply costs have all chipped away at the administrative line of cooperative group budgets. Cooperative groups can no longer rely on other sources of funding to offset the increasing annual budget deficit related to participation as CCOPs research bases. The cooperative groups remain committed to the aims of the CCOP program but must be supported through a different calculus if they are to continue to participate in this program.

If resources could be identified, the development of a national data base formed by identifying representative cancer patients not participating in clinical trials and monitoring them from diagnosis would provide a

method to judge the impact of the cancer clinical trials program on oncology practice in the United States.

The Review Group believes that the award for the operations of cooperative groups should no longer be calculated based on credit accrual using a fixed capitation rate, as the costs of supporting CCOP do not directly relate to actual patient accrual rates. Instead, the overwhelming majority of the functions associated with operations are directly related to the size of the CCOP membership affiliated with the Group. Regardless of the fluctuations of accrual funding rates, the operations offices must perform at a level proportional to the needs of the CCOP institutions and consortium members in meeting the stated goals of the CCOP program. The Review Group is aware that the cooperative group chairs are currently examining the operations offices and staffing of the statistical centers to determine ways to increase fiscal and administrative efficiency, and that detailed recommendations might be forthcoming from that examination. The Review Group makes the following recommendations.

- Future funding for cooperative group operations should be based on the costs of performing as a headquarters office, and proportional to CCOP membership.
- Therapeutic trials conducted through the CCOP mechanism should be transferred to the Division of Cancer Treatment, Diagnosis and Centers. Cancer prevention studies conducted across the NCI clinical trials system should be the responsibility of a newly configured Division of Cancer Prevention and Control.

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Clinical Trials Program Review Group Meeting Presenters

Dr. Martin Abeloff	Dr. Joseph R. Huguenard
Dr. Carmen Allegra	Dr. Andrew Kelahan (2)
Dr. James O. Armitage (3)	Dr. David King
Dr. Joseph Bailes	Dr. Richard Klausner
Dr. Archie Bleyer (2)	Dr. Barry Kramer
Dr. Carla Bloomfield	Dr. Allen Lichter
Dr. Otis Brawley	Dr. Marc E. Lippman
Col. Doris Browne	Dr. David Livingston
Dr. Vincent Cairoli	Dr. James Lynch
Dr. Paul Calabresi	Mr. Michael Larcos

Dr. Thomas R. Caldwell	Dr. Worta McCaskill-Stevens
Dr. George Canellos	Dr. Sandra Millon-Underwood
Dr. Charles Cobau	Dr. John D. Minna
Dr. C. Norman Coleman	Dr. Edward V. Morse
Ms. Deborah Collyar (2)	Dr. Sharon Murphy - conference call
Dr. Charles A. Coltman, Jr. (3)	Dr. Larry Norton
Dr. Robert Comis	Dr. Richard O'Reilly
Dr. James Cox (2)	Dr. David Parkinson
Dr. Robert J. Delap	Dr. Marcel Rozencweig
Dr. Kay Dickerson	Dr. Aurther Rubenstein
Dr. John Falletta	Dr. Philip Schein
Dr. Louis Fehrenbacher	Dr. Steven H. Sheingold
Dr. John Fetting	Dr. Faina Shtern
Dr. Leslie Ford (2)	Dr. Joseph Simone
Dr. Michael Fordis	Dr. Robert J. Spiegel
Dr. Steven C. Fox	Dr. Philip Steuber
Dr. Emil Freireich	Dr. Katrina Timson
Dr. John A. Gilley	Dr. Richard Ungerleider
Dr. John Glick	Ms. Emily Untermeyer
Dr. Michael N. Gould	Dr. Ralph Vogler
Dr. Michael Glode	Dr. Daniel D. Von Hoff
Dr. Peter Greenwald	Dr. Samuel A. Wells, Jr.
Dr. David Harrington	Dr. Carol Westbrook
Dr. Gerri A. Henwood	Dr. Robert Wittes
Dr. Henry Hynes	Dr. Roger Winn
	Dr. William Wood

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Meetings of the Review Group

The review group met on the following dates:

April 8, 1996

September 16-17, 1996

October 14-15, 1996

November 25-26, 1996

January 27-28, 1997
March 10-11, 1997

¹ This committee, chaired by David Nathan, has not yet released its final report. (back)

² Institute of Medicine. 1994. Careers in Clinical Research: Obstacles and Opportunities. Washington, D.C.: National Academy Press. (back)

³ Emil J. Freireich. 1991. A study of the status of clinical cancer research in the United States. Journal of the National Cancer Institute 83:829-837. (back)

⁴ Pediatric Hematology-Oncology Manpower Projections, U.S.A. (The Buchanan Report). Presented by Archie Bleyer at the October 15, 1996 meeting of the Review Group. (back)

⁵ An Analysis of the Review of Patient-Oriented Research (POR) Grant Applications by the Division of Research Grants, National Institutes of Health by the Clinical Research Study Group, November 21, 1994. (back)

⁶ National Cancer Institute. 1996. *Recruitment and Retention of Minority Populations in Clinical Cancer Research: Conference Summary--January 26-27, 1996*. (back)

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