Report of the Clinical Trials Working Group of the National Cancer Advisory Board

Restructuring the National Cancer Clinical Trials Enterprise

June 2005

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Executive Summary

In January 2004, Dr. Andrew von Eschenbach, Director of the National Cancer Institute (NCI), established the Clinical Trials Working Group (CTWG) to advise the National Cancer Advisory Board (NCAB) on whether and in what ways the NCI-supported national clinical trials enterprise should be restructured to realize the promise of molecular medicine for advancing oncologic clinical practice in the 21st century. The CTWG is a broadly constituted panel with experts from academic research institutions, community oncology practices, the pharmaceutical and biotechnology industries, cancer patient advocacy groups, NCI, the Food and Drug Administration (FDA), and the Centers for Medicare and Medicaid Services (CMS).

The CTWG first reached consensus on four critical goals for designing a restructured national clinical trials enterprise that is not only more efficient and coordinated but founded on the best science. The first goal was to improve coordination and cooperation among the functionally diverse components of the current system, including industry and federal regulatory agencies. The second goal was to improve prioritization and scientific quality by developing an open and transparent process for the design and prioritization of clinical trials that are science-driven and meet the needs of patient care. The third goal was to improve standardization of tools and procedures for trial design, data capture, data sharing, and administrative functions to minimize duplication of effort, and to facilitate development of a shared infrastructure to support an integrated national cancer clinical trials network. The fourth goal was to improve operational efficiency by increasing the rate of patient accrual and reducing operational barriers so that trials can be initiated and executed in a timely, cost-effective manner.

In addressing these goals, the CTWG proceeded through a consensus building process involving three sequential stages. First, the CTWG defined which specific aspects of the current system could and should be improved. The second stage focused on development of recommendations to address those improvements; these recommendations were presented to the NCAB on February 17, 2005. In the third stage, the CTWG defined specific initiatives based on those recommendations and designed implementation plans for their practical realization.

The result of this broad-based, strategically-driven effort, involving all the critical stakeholders in the cancer clinical trials community, is the compendium of 22 initiatives detailed in this report on "Restructuring the National Cancer Clinical Trials Enterprise." The proposed initiatives cover a wide range of specific components of the current system, and each addresses one of the common themes derived from the CTWG goals: Coordination, Prioritization/Scientific Quality, Standardization, or Operational Efficiency. These initiatives are designed to support a powerful and transparent clinical trials enterprise that integrates the individually strong components of the current system into a cross-disciplinary, scientifically-driven, cooperative research effort. Because this enterprise will also require coordinated leadership, the CTWG recommends two

Enterprise-Wide initiatives addressing ongoing NCAB oversight of clinical trials and an integrated NCI organizational structure for clinical trials management.

The initiatives, which are described in detail in the report, are summarized below.

Coordination Initiatives

- Create a comprehensive database containing information on all NCI-funded clinical trials to facilitate better planning and management across clinical trial venues.
- Realign NCI and academic incentives to promote collaborative team science.
- Increase cooperation between NCI, FDA, and industry to enhance the focus and efficiency of oncology drug development.
- Expand awareness of the NCI-FDA expedited approval process to speed trial initiation.
- Work with CMS to identify clinical studies that address both NCI and CMS objectives, and for which CMS may be able to reimburse some routine and investigational costs.

Prioritization/Scientific Quality Initiatives

- Create an Investigational Drug Steering Committee to work with NCI to enhance the design and prioritization of early phase drug development trials.
- Create a network of Scientific Steering Committees, which leverage current Intergroup, Cooperative Group, Specialized Programs of Research Excellence (SPORE), and Cancer Center structures, to work with NCI in the design and prioritization of phase III trials to better allocate scarce resources, improve scientific quality, and reduce duplication.
- Increase community oncologist and patient advocate involvement in clinical trial design and prioritization to improve the rate of patient accrual, and better address practical and quality of life concerns in the design of trials.
- Develop a funding and prioritization process to ensure that critical correlative science and quality of life studies can be conducted in a timely manner in association with clinical trials.
- Develop a standards-setting process for the measurement, analysis, and reporting of biomarker data in association with clinical trials to enhance data comparisons, reduce duplication, and facilitate data submission for regulatory approval.
- Investigate integration of phase II trials into the overall prioritization process to further coordinate the national clinical trials system.

Standardization Initiatives

- Create, in partnership with the extramural cancer research community, a national cancer clinical trials information technology infrastructure fully interoperable with NCI's cancer Bioinformatics Grid to improve cost effectiveness and comparability of results across trials and sites.

- In consultation with industry and FDA, develop standard Case Report Forms incorporating Common Data Elements to improve information sharing among cancer researchers and optimize data requirements.
- Build a credentialing system for investigators and sites recognized by NCI and industry to allow faster trial initiation and keep the investigative community abreast of legal, safety, and regulatory changes.
- Develop commonly accepted clauses for clinical trial contracts with industry to reduce the lead-time needed to open trials.

Operational Efficiency Initiatives

- Restructure the phase III funding model to promote rapid patient accrual rates and cost-effectiveness.
- Reduce institutional barriers to timely trial initiation.
- Increase patient and public awareness and understanding of clinical trials.
- Increase minority patient access to clinical trials to improve the participation of underserved and underrepresented populations.
- Promote adoption of the NCI Central Institutional Review Board facilitated review process to reduce the time and resources needed to open trials at individual sites.

Enterprise-Wide Initiatives

- Create a Clinical Trials Oversight Subcommittee of the NCAB to advise the NCI Director on conduct of clinical trials across the Institute.
- Develop a coordinated NCI organizational structure to manage the entire clinical trials enterprise supported by the Institute.

No major restructuring of an ongoing enterprise such as NCI-supported cancer clinical trials should be undertaken without a plan to evaluate its success. Therefore, the CTWG has also proposed that a formal system be developed to evaluate the success of the restructuring effort. The evaluation system will address three important measures. The first measure is program management to track and evaluate implementation of the initiatives. The second measure is system performance to evaluate the effect of the restructuring on the design, prioritization, and conduct of cancer clinical trials. The third measure is system outcomes to assess the effect of the restructuring on increasing the number of useful therapies for patients and improved targeting of therapies to the patients most likely to benefit from them.

Each of the initiatives is accompanied by an implementation plan including an associated timeline and budget. Implementation of the CTWG initiatives will require four to five years to complete, although the majority are targeted for implementation by the end of year three. Bringing the initiatives forward into routine practice will then require an additional two to three years. The restructuring effort is projected to cost $113M over five years. Projected expenses increase from $7.1M in FY06 to $20.6M in FY07 reaching a steady state of approximately $29M annually in FY08 and beyond. Of this

annual total, 75% is direct support to the extramural community, 10% is for the comprehensive clinical trials database, 10% is to operate the extramurally-driven prioritization process, and 5% is for the NCI management structure necessary to effectively guide this new enterprise.

Implementing these initiatives will require considerable additional effort by the extramural clinical trials community, as well as an increased financial investment by NCI. But such new commitment and investment will result in an increased level of ownership in and responsibility for the clinical trials system by all of its stakeholders, and is crucial for ensuring that the large, ongoing national investment in cancer clinical trials achieves the goal of bringing effective new therapies to patients. By embracing this restructuring, NCI and the oncology community will be positioned to ensure that the advances in understanding the biological basis of cancer, generated by the past 40 years of research, make a substantive difference in reaching the NCI 2015 goal of eliminating suffering and death from cancer.

Summary Vision

Enhance the best of all the components of the NCI-supported clinical trials system to develop a cooperative enterprise built on a strong scientific infrastructure and a broadly engaged coalition of critical stakeholders.

Advances in molecular medicine offer enormous potential to improve cancer clinical practice by moving beyond the cytotoxic treatments of the past to safer and more effective therapies targeting the specific characteristics of a patient's tumor. However, development of these targeted therapies, based on an understanding of the genetic and cellular mechanisms underlying specific cancers, creates several challenges for the design and conduct of cancer clinical trials.

Trials driven by advances in cancer biology will require robust clinical trial designs that necessitate comprehensive information sharing and close collaboration among clinical researchers and basic and translational scientists. Moreover, the evaluation of novel targeted therapies, designed to be effective against cancers with a specific molecular profile, depends on synergistic integration of treatment protocols with modern molecular diagnostic and imaging techniques. Such integration will require real-time, coordinated participation between clinical oncologists and experts in comprehensive molecular analysis and bioinformatics during the conduct of trials. Therapies appropriate for only a subset of patients will also require a large, coordinated network of institutions and clinical investigators to achieve adequate and timely patient recruitment. It may be difficult for single institutions or even existing networks and groups to be successful on their own. And finally, the rapid pace of scientific progress has created an ever-increasing number of novel therapies to test. Only through an open, collaborative prioritization system involving all the critical stakeholders can the best decisions be made as to which agents and disease targets warrant an investment of taxpayer dollars in clinical trials.

This enormous potential for more specific cancer treatment, coupled with the complexity of evaluating new, highly specific agents, requires a national clinical trials enterprise that integrates the knowledge, insights, and skills of multiple fields into a new kind of cross-disciplinary, scientifically-driven, cooperative research endeavor. Creating such an endeavor will require integration of the successful, but functionally diverse, elements of the current clinical trials system supported by the National Cancer Institute (NCI). The strength of the current system is that it involves many institutions across the public, private, and academic sectors as well as a broad cross-section of clinical investigators and other healthcare professionals. The challenge is to bring these diverse institutions and individuals together into an integrated and efficient, but innovative and responsive, engine for moving therapies to patients.

Building a national clinical trials enterprise founded on the best science requires the achievement of four important goals. The first is to enhance coordination and cooperation by ensuring that comprehensive information on cancer clinical trials is readily available for all stakeholders, that collaborative team science, as well as individual achievement, is rewarded, and that NCI clinical trials are effectively coordinated with federal regulatory systems. The second is to enhance scientific quality and prioritization so that NCI supports the best-designed trials, addressing the most important questions, leveraging the most significant scientific advances. The third is to enhance standardization of tools and procedures for trial design, data capture, data sharing, and administrative functions to decrease effort and minimize duplication. The fourth is to enhance operational efficiency by increasing the rate of patient accrual and reducing operational barriers so that trials can be initiated and executed in a timely, cost effective manner.

To address these challenges and goals, the Clinical Trials Working Group (CTWG) of the National Cancer Advisory Board (NCAB) has developed a detailed blueprint for "Restructuring the National Cancer Clinical Trials Enterprise" so that the translational power of individualized oncologic medicine can drive clinical trials research in the 21st century. The strategy developed by the CTWG focuses on leveraging the unique strengths of the current clinical trials enterprise. It is a strategy that specifically recognizes the role of NCI-designated Cancer Centers as the primary institutional home for a large number of cancer clinical investigators, the strength of Specialized Programs of Research Excellence (SPOREs) in disease-oriented translational studies, the critical need for investigator-initiated clinical trials supported by Program Project (P01) and R01 Grants, the stable clinical trials infrastructure provided by the Cooperative Groups, and the ability of Community Clinical Oncology Programs (CCOPs) and other community oncologists to provide clinical trials in a local environment. The proposed restructuring preserves and strengthens all of these existing components of the NCI clinical trials system, but asks them to work together in fundamentally different ways.

Cooperative Groups, Cancer Centers, SPOREs, and individual investigators will be asked to participate collaboratively in a joint enterprise guided by scientific priorities and informed by input from basic and translational scientists, community oncologists, and patient advocates. Sharing of data and ideas, and the development of true team science will become a new standard of excellence alongside individual and institutional achievement. NCI staff and extramural investigators will be asked to develop a closer relationship based on an open sharing of ideas that will enhance the design of cancer clinical trials. Industry and government regulatory agencies will also be asked to become active participants in the collaborative enterprise. And finally, the extramural community will be called upon to make a significant commitment to assist in the governance of the new enterprise, working side by side with NCI to set new policies, procedures, and standards, and guide prioritization and decision-making.

Implementing these changes will require considerable effort by all stakeholders as well as new financial investment. But this renewed commitment and the associated resources are

crucial for ensuring that the large, ongoing national investment in cancer clinical trials achieves the goal of bringing effective new therapies to patients. By embracing this restructuring, NCI and the oncology community will be positioned to ensure that the advances in understanding the biological basis of cancer, generated by the past 40 years of research, are harnessed effectively to bring measurable, meaningful benefits to patients as NCI pursues the goal of eliminating suffering and death from cancer by 2015.

Introduction

In January 2004, Dr. Andrew von Eschenbach, Director of the National Cancer Institute (NCI), established the Clinical Trials Working Group (CTWG) to advise the National Cancer Advisory Board (NCAB) on the development, conduct, infrastructure, support, and coordination of cancer clinical trials across the NCI. The charge to the CTWG was to develop recommendations and an implementation plan to optimize the NCI-supported clinical trials system by improving coordination and research infrastructure, by removing institutional and regulatory barriers that inhibit collaboration in clinical trials research, and by envisioning how clinical trials should be conducted utilizing the tools of contemporary bioinformatics and molecular medicine. The CTWG is a broadly constituted panel with experts from academic research institutions, community oncology practices, the pharmaceutical and biotechnology industries, cancer patient advocacy groups, NCI, the Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS). The membership of the CTWG is provided at the front of this report.

In approaching its objectives, the CTWG built on extensive prior analysis and recommendations for improving the NCI-supported cancer clinical trials system developed by the 1997 "Report of the NCI Clinical Trials Program Review Group" (Armitage Report) and the subsequent 1998 "Report of the National Cancer Institute Clinical Trials Implementation Committee," as well as several feedback reports on the success of these efforts. In addition, the CTWG examined in detail the 2003 report of the P30/P50 ad hoc working group, "Advancing Translational Cancer Research: A Vision of the Cancer Center and SPORE Programs of the Future" so that the critical role of both the Specialized Programs of Research Excellence (SPOREs) and NCI-designated Cancer Centers in the cancer clinical trials process would be part of the framework for its restructuring effort. In this way, the overall organization of the current NCI-funded clinical trials system was reviewed, providing the essential background for the work of the CTWG.

The CTWG conducted seven face-to-face meetings and ten group conference calls from January 2004 through May 2005. Meeting dates and acknowledgments appear in Appendix A. In addition, the CTWG subcommittees responsible for the development of the formal recommendations and implementation plans conducted a substantial number of additional conference calls among themselves and with ad hoc experts to refine their proposals. Furthermore, during this process, the extramural community provided substantive, real-time input into the development of the CTWG's recommendations through its response to questions about draft recommendations posted on a CTWG internet-based forum that elicited over 2200 responses.

The CTWG reached consensus through three sequential stages. The first stage was to define which aspects of the current system should be improved. The second stage was to develop recommendations for addressing those improvements; these recommendations

were presented to the NCAB on February 17, 2005. The third stage was to define new initiatives based on these recommendations and to design implementation plans that are innovative, yet practical, and which harness the best of the current clinical trials system.

The result of this consensus building process is the 22 initiatives detailed in this report on "Restructuring the National Cancer Clinical Trials Enterprise." The proposed initiatives are organized into five categories: Coordination, Prioritization/Scientific Quality, Standardization, Operational Efficiency, and Enterprise-Wide.

The Coordination Initiatives are directed at enhanced information sharing, incentives for collaborative team science, and coordination of regulatory processes. The Prioritization/Scientific Quality Initiatives establish new processes for the design and prioritization of clinical trials, and for facilitating the conduct of correlative science and other ancillary studies. The Standardization Initiatives promote development of standardized tools and procedures to minimize duplication and reduce the effort required to initiate and conduct clinical trials. The Operational Efficiency Initiatives focus on improving patient accrual rates and reducing operational barriers to speed both the initiation and conduct of clinical trials. The Enterprise-Wide Initiatives address restructuring the management and oversight of NCI's clinical trials program both from within the NCI and in partnership with the extramural community.

In each section, the initiatives are organized into two categories. New Initiatives propose a fundamental and significant change in the operation of the current NCI clinical trials system. Enhancement Initiatives include those initiatives that propose an expansion or enhancement of an activity already underway within the Institute. Each initiative includes an implementation plan as well as an associated timeline and budget. The timelines and budgets are presented in a consolidated Timeline and Budget section.

No major restructuring effort should be undertaken without establishing a mechanism for evaluating its success. Accordingly, the report includes a section on Evaluation and Outcomes that outlines the process recommended by the CTWG for evaluating the success of the restructuring effort.

Coordination Initiatives

Introduction:

The CTWG addressed three key dimensions of coordination: enhanced information sharing, alignment of incentives to facilitate improved collaboration, and coordination of regulatory strategies and procedures with the scientific enterprise. Improvement in all these areas is essential to achieve the ultimate goal of delivering important new cancer therapies to patients more quickly.

The CTWG envisions an enhanced cancer clinical trials enterprise in which increased participation by the extramural community in the prioritization process more effectively focuses resources on those trials judged most likely to facilitate advances in treatment. The success of this strengthened prioritization process depends on a shared foundation of comprehensive, up-to-date information about the status of cancer clinical trials.

The productivity of the national cancer clinical trials enterprise will also depend increasingly on collaborative team science. However, the incentives implicit in NCI's current modes of evaluating program accomplishment, making grant or contract renewal decisions, and allocating funds are not fully congruent with the needs of collaborative science. The cancer clinical trials enterprise has always benefited enormously from the *pro bono* spirit shared by cancer investigators who are dedicated to improving the lives of cancer patients. The system will function more effectively in the future if NCI can assure that institutional and professional rewards will accrue to those who participate collaboratively in the enterprise as a whole.

Finally, both the FDA and CMS are intimately involved in the process by which new treatments are brought to market, and adopted and utilized by physicians. Close and continuous interaction between NCI and these partners will facilitate the development and utilization of new cancer therapies, while at the same time protecting patient safety.

For the nation's cancer clinical trials system to fulfill its promise, the supporting information systems, incentive structures and regulatory processes must be updated and coordinated to address the new needs and opportunities of cancer research today. The CTWG proposes five initiatives to achieve this goal; two of these are entirely new, and three will substantively enhance current or recently-developed activities.

New Initiatives:

1. Establish a comprehensive database containing regularly-updated information on all NCI-funded clinical trials.

2. Realign NCI funding, academic recognition, and other incentives to promote collaborative team science and clinical trial cooperation.

Enhancement Initiatives:

1. Develop guidelines and procedures for joint participation of FDA and NCI in meetings, including those with industry, concerning new agents and diagnostics.

2. Increase awareness of the NCI-FDA expedited concept/protocol approval process, including use of the FDA Special Protocol Assessment.

3. In collaboration with CMS and other payers and stakeholders, establish a robust and transparent process for identifying clinical studies that might have routine and clinical costs supported using traditional reimbursement mechanisms.

New Initiative 1:

Establish a comprehensive database containing regularly-updated information on all NCI-funded clinical trials.

Rationale:

An electronic database containing complete, up-to-date information about the status of all cancer clinical trials would be extremely valuable to the clinical trials community. Benefits include the following:

- When preparing new trial concepts and proposals, investigators could take into account other trials already completed or underway addressing similar questions, and thus eliminate unnecessary duplication of effort.
- Prioritization would be enhanced by having available a full picture of the cancer clinical trials enterprise.
- Patient accrual to trials would be enhanced because physicians and patients would be aware of relevant opportunities for participation in clinical trials.
- Potential patient harm would be reduced because toxicity and adverse events that are recognized in active trials would be rapidly disseminated to other investigators and practicing clinicians.
- Patients would benefit because patterns of favorable outcomes that are recognized in active trials would be rapidly disseminated to the clinical trials community.

Among currently available public resources supported by the NCI, the one that most closely approximates the resource envisioned is the clinical trials database within NCI's PDQ system. However, this database falls short in several important respects.

First, PDQ's listing is incomplete. NCI-funded trials in four sponsorship categories – Cancer Therapy Evaluation Program (CTEP), Cooperative Groups, the NCI intramural

Center for Cancer Research (CCR), and the Division of Cancer Prevention (DCP) – are submitted automatically, as are those conducted by the European Organization for Research and Treatment of Cancer (EORTC). Submission of all other trials, including those performed by Cancer Centers, SPOREs, and investigators supported by the R01, R21, or P01 mechanisms, is voluntary.

Moreover, the database in PDQ is intended primarily to facilitate patient recruitment, and therefore focuses on the information necessary to identify protocols for which a patient may be eligible. Accordingly, PDQ does not include the results of clinical trials. It does not collect either individual or summary patient-level data and does not provide a source of trial outcome information. It is thus of limited value to investigators designing new trials.

Data on the results of certain clinical trials are currently collected by several different administrative units within the NCI. However, the specific data content and its format varies widely between these units. It is therefore not possible to electronically share data between NCI divisions, nor is it possible to provide electronically accessible data, even in anonymized, summary form, to the research community.

Finally, none of the current NCI clinical trials databases reflect up-to-date principles of information systems design. They are not based on the structured data, standardized interfaces and modular architecture that would facilitate utilization across the entire cancer clinical trials enterprise. The infrastructure provided by the NCI's cancer Bioinformatics Grid (caBIG) is founded on these principles and can serve as a blueprint for the construction of the recommended database.

The new database will be more than a convenience. Because of its role as the sponsor of a large number of cancer clinical trials implemented across a wide range of venues, NCI is uniquely positioned to take a global view of emerging knowledge from cancer trials, and to identify important patterns and insights in a timely way. Routine review of safety, efficacy, and administrative data reported from ongoing NCI-funded clinical trials is essential to the timely recognition and appropriate dissemination of emerging insights on the safety and efficacy of new treatments, while also assuring that NCI's resources are invested productively, and that its program planning and prioritization activities are based on the best and most recent available data.

At present, this review of incoming data is constrained both by the absence of comprehensive data reporting and by limited capacity to evaluate such data critically. To assure patient safety and an optimal return on the nation's investment in cancer clinical trials, it is imperative not only that the completeness of data reporting be assured, but that sufficient capacity to monitor incoming data from all sponsored trials be present.

Implementation Plan:

Content of the Database

Studies. The database will include all NCI-funded clinical trials, regardless of drug development phase, type of intervention or treatment, study design, or program through which funding is provided. A long-term goal is to include information on trials funded by other public- and private-sector sponsors, including studies by other National Institutes of Health (NIH) institutes that have cancer-related endpoints specified prospectively (e.g., Women's Health Study), and studies funded by the Department of Defense, the pharmaceutical industry, and private foundations. All trials entered into the database will be maintained in the database indefinitely, so that both active and completed studies will be included.

To facilitate rapid progress on the most pressing coordination needs of the national cancer clinical trials enterprise, the CTWG recommends that the first priority for inclusion in the new database be trials of pharmacologic, biological, surgical and radiation interventions, beginning with phase III trials and followed by phase II and phase I studies. As soon as practical, the database will be extended to include comprehensive information on trials of supportive care, behavioral interventions, screening and detection.

Data Elements. For each trial, the database will include descriptive information about the trial protocol and accrual status, as well as contact information for those who have further questions or wish to participate in the trial. All key elements of the existing PDQ system will be preserved, including the special overviews and summaries drafted for lay readers. In addition, the database will include a standard set of data elements collected during the trial. This data set will include all data elements currently in the NCI Clinical Data Update System (CDUS) comprehensive data set, the data currently shared in briefing books prepared for Cooperative Group meetings, summary information on adverse events, toxicity and efficacy, and links to any results published, presented in public, or issued as an advisory by Federal agencies including NCI and FDA.

Database Functions

Search and Reporting. The database will be equipped with software tools that allow searches on any field or combination of fields, using any keywords or combination of keywords. Searching will be facilitated with pre-defined menus of keyword options wherever appropriate (e.g., cancer type, treatment type, etc.). Both interactive and batch-mode reporting will be supported, and predefined report templates will be available.

Access Control. Access privileges will be defined to address the diverse needs of different users of the database. Three user categories are envisioned. "General" users (including practicing clinicians, patients, caregivers, patient advocates, and other interested parties) will have access to descriptive data about study protocols, accrual status, summary data on findings, and alerts approved for public release. Cancer clinical investigators will have access to "briefing book" data as well as access to all data available to general users. For phase III trials, primary outcome data and secondary outcomes that might influence trial participation will not generally be available until trial data are released by the Data and Safety Monitoring Board (DSMB) for the study. NCI

program staff will have access to all data in the repository, including raw data as submitted as well as all data accessible to all other user categories.

System Implementation

Management Responsibility. The NCI Center for Bioinformatics (NCICB) will be responsible for management and oversight of system implementation. Actual implementation of different components of the system may be carried out by NCI staff, contractors or other external partners as appropriate.

Design Principles. The database will be implemented in accordance with caBIG design principles and implementation standards. These standards, including the use of standard vocabularies and data elements, modular architecture, and standard programming and data exchange interfaces, will provide maximum power, flexibility and adaptability to meet the needs of the cancer clinical trials community both today and in the future.

The central data repository will not necessarily reside in one physical location. If appropriate, other data resources internal and external to NCI can be incorporated through appropriate data retrieval links. However, such links will be designed to operate automatically and will be invisible to the user, who will perceive a single, unified "virtual" database. User tools will be accessed through web-based interfaces, with each interface designed to maximize ease of use for the intended user group.

Implementation Task Force. NCI will establish an implementation task force of clinical investigators, community oncologists, biostatisticians, and patient advocates to provide input on data submission procedures, access privileges for different types of users, user interface needs, user tool specifications, and testing and revision of user tools. In consultation with the task force, NCICB will conduct interviews, focus groups, or other research as needed to define user-friendly interfaces for investigators and other user groups, and will conduct pilot testing with extramural users prior to system roll-out.

Relationship to Other Cancer Trial Databases. The database is intended to be the primary clinical trials information tool provided by NCI to support investigators, practicing clinicians, and lay users. Once it is implemented, NCI will not invest resources in duplicative data repositories. However, as is the case with existing clinical trials data repositories, it is expected that there will be outside groups who wish to provide access to database content through distinctive user interfaces that address the needs of special audiences. Construction of the database according to caBIG principles will allow NCI to grant qualified outside groups the right to develop independent software tools that access selected data from the repository and present it through distinctive search and reporting interfaces, in accordance with established access policies and controls.

Data Submission Procedures and Policies

Data Submission Procedures. Procedures for data submission will be designed by NCICB in consultation with NCI program staff and representatives of the extramural investigator community on the implementation task force. The goal is to incorporate data submission into typical investigator workflows with minimal added burden such that investigators submit required data to NCI only once, and NCI manages distribution to all NCI staff who need access. In some cases, where appropriate standards for data systems design have been implemented locally, it may be appropriate for "submission" to occur via a link to a local data repository rather than through physical transmission to the central repository.

Data Submission Policies. Reporting of data required for the database will be a routine obligation for all NCI studies, regardless of funding mechanism. For programs implemented via cooperative agreements, program guidelines will be updated to specify data reporting requirements and to define required data reporting as an allowable cost. For programs implemented via grants, NCI will seek counsel from appropriate authorities within NCI and the Office of Management and Budget (OMB) to specify a data reporting requirement in compliance with Federal regulations governing grants, and to assure that such data reporting requirements are allowable expenses. Furthermore, the CTWG recommends that funds be made available to accommodate the initial costs incurred for additional data reporting requirements prior to cooperative agreement, grant, or contract competitive renewal.

NCI Review of Data

To implement timely review of this expanded data set, new NCI oncology staff members, as well as expansion of existing contractor support, will be required. As the new clinical trials database is implemented, NCI will evaluate the potential for new software tools associated with the database to facilitate the required logistical support.

New Initiative 2

Realign NCI funding, academic recognition, and other incentives to promote collaborative team science and clinical trial cooperation.

Rationale:

It is widely recognized that current incentives within the national cancer clinical trials enterprise, both those implicit in NCI project selection and funding practices, and those implicit in academic institutions' criteria for academic promotion and honors, do not encourage cooperative efforts to bring new therapies to patients. These incentives can be realigned in two primary ways. The first is to modify NCI competitive award mechanisms to give appropriate credit for participation in collaborative clinical trials and to provide adequate resources to all investigators participating in such trials. The second

is to modify academic institutional practices to increase the value accorded to active participation in federally-funded clinical trials during faculty performance evaluations.

Current patterns of academic recognition are deeply rooted in the culture and management practices of academic institutions, and inducing cultural change in such powerful, autonomous and managerially conservative institutions will be a challenge. While NCI does not directly control the behavior of academic institutions, nor should it, it is important for the Institute to catalyze the process of change by realigning those incentives that are within its control to send a clear message as to the importance of collaborative science in bringing effective new treatments to patients.

One of the most powerful tools at NCI's disposal is the set of criteria used to determine whether awards will be made or renewed. Funding decisions have enormous implications for an institution, both financial and otherwise. It is imperative that award guidelines be updated to reflect NCI's best current understanding of the practices needed to advance cancer clinical research most effectively.

Although research funding is a potent incentive at the institutional level, NCI should also take steps to facilitate the recognition of clinical trial participation within academic institutions' career advancement mechanisms. NCI leadership should work to engage academic institutions in a fundamental review of the principles underlying career advancement policies and in defining appropriate adjustments to those policies.

The ultimate goal is a shared culture in which investigators collaborate freely across disciplines, institutions, and programs wherever this is needed to most expeditiously advance the design and conduct of cancer clinical trials.

Implementation Plan:

Award Guidelines

NCI program award guidelines and scoring systems will be revised to allocate credit for the behaviors needed to advance collaborative science. The objectives of these modifications will include the following:

1. Reward collaborations among Cancer Centers, SPOREs, P01s, R01s, early clinical trials networks, Cooperative Groups and other NCI-supported multisite clinical trials networks that advance concepts from pilot studies to Phase III trials and provide correlative science services for large, multisite studies.

2. Reward Cooperative Groups and other NCI-funded clinical trials networks for broad participation in multisite trials conducted throughout the NCI-supported clinical trials system.

3. Reward efforts to move innovation forward through the most effective and expeditious means, including handoffs between various NCI-funded programs where appropriate.

Funding Practices

NCI funding practices will also be examined for opportunities to incentivize collaborative science. Examples might include reimbursement for SPORE and Cancer Center clinical trials that accrue patients through the NCI's Cancer Trials Support Unit (CTSU), and travel and expense reimbursement for non-PI investigators to attend planning and coordination meetings for trials.

New Forms of Recognition for Cancer Clinical Investigators

NCI will create a new "Cancer Clinical Investigator Team Leadership Award" for mid-level clinical investigators not currently holding Principal Investigator status on an NCI grant. The award, which would provide funding equivalent to 10-20% salary support per year, will be competitive, with nominations submitted annually by Cancer Centers or other institutions carrying out NCI-funded clinical trials. The intent is to reward exceptional contributions that advance effective new treatments toward practice and embody the ideals of collaborative team science. NCI will also conduct informal consultations, focus groups, and surveys to identify additional forms of recognition that could be awarded by NCI and that would be valued by investigators and their institutions.

Academic Reward Practices

NCI and NIH leadership will work proactively with the Association of American Medical Colleges (AAMC), the Institute of Medicine (IOM) and other organizations to persuade medical school deans of the need to adjust their institutions' incentive structures to reward collaborative clinical research.

Enhancement Initiative 1:

Develop guidelines and procedures for joint participation of FDA and NCI in meetings, including those with industry, concerning new agents and diagnostics.

Rationale:

The great need for improved cancer therapies, the long and expensive research and development process for new drugs, and the large number of candidate drugs generated by advances in fundamental research make it imperative to reduce inefficiencies in the process by which new drugs are tested and approved for marketing.

Improved interaction between NCI, industry, and FDA would save time, effort and resources in bringing new cancer therapeutic agents to market. Beneficial outcomes would include clinical trial strategies and protocols that better meet FDA standards, higher quality FDA submissions based on results from NCI-funded trials, and greater focus of NCI-funded clinical research on drug candidates that are likely to meet FDA requirements for marketing approval.

In 2003, NCI and FDA created a framework for enhanced collaboration in the Interagency Oncology Task Force. The Task Force has been addressing a range of issues of mutual interest, most notably strengthening the infrastructure for cancer clinical trials and new drug evaluation. The CTWG initiative seeks to build on this foundation and further promote interaction between NCI, FDA, and industry in the development of new agents, with the goal of improving the focus, efficiency, and timeliness of oncology drug development.

Implementation Plan:

FDA-industry meetings. NCI representatives will be included in meetings for all agents for which NCI has a Clinical Trial Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA) with the sponsor, and sponsors will be encouraged to include NCI representatives in meetings even when NCI does not have a CTA or CRADA.

NCI Drug Development Group meetings. Special liaison representatives from FDA will be included to better inform the FDA about new agents that are in the earliest stage of preclinical development by the NCI.

NCI meetings with industry to review new agents. Sponsors will be encouraged to include FDA representatives in these meetings.

Operating procedures and guidelines for joint meeting participation will be developed. A key requirement is to create policies and procedures that promote free and open sharing of knowledge and insights, while assuring industry that proprietary information will remain confidential and that interactions with FDA will not prejudice later regulatory proceedings. It will also be necessary to assure that FDA can continue to respond to any new, safety-critical information in accordance with its mandate.

These proposals have already been placed on the agenda of the FDA and the Interagency Oncology Task Force for review and refinement. Plans are underway to obtain broad input from the pharmaceutical and biotechnology industries as well. FDA and industry support is necessary to assure that joint FDA/NCI meeting participation enhances the drug development process rather than complicates it to no material benefit.

It should be noted that the new guidelines are not meant to be rigid. Industry will always retain the right to decline broader involvement when such involvement is felt to be

inappropriate, and NCI and FDA will, as always, need to prioritize the use of available staff time. However, the intent is to establish the proposed broader meeting participation as the standard.

Enhancement Initiative 2:

Increase awareness of the NCI-FDA expedited concept/protocol approval process, including use of the FDA Special Protocol Assessment.

Rationale:

For NCI-funded trials that could lead to a licensed indication, the NCI and FDA have developed a process whereby a concept, once approved by NCI, will receive a rapid review (two to three weeks maximum) by the FDA. Based upon this initial FDA review, a series of informational exchanges ensue between the FDA and those conducting the trial (the Cooperative Group, company-sponsor, and NCI) until a consensus is reached on a trial design that will meet FDA requirements for registration. Following this consensus, the protocol is developed using NCI's expedited protocol development process, and the company sponsor, if it so chooses, can also submit the protocol to the FDA for a Special Protocol Assessment (SPA).

An approved SPA documents the FDA's binding agreement that the design and planned analysis of a study adequately addresses the objectives in support of a regulatory submission (for phase III Cooperative Group trials, this is usually an efficacy claim). Although the SPA process is available to all industry sponsors, the FDA has agreed to work with NCI to complete the review of NCI Cooperative Group trials in an even more rapid fashion since the Agency will have reviewed the trial at the concept stage. This process allows the Cooperative Group, its industry partners, and the NCI to proceed expeditiously in preparation of a final protocol document without the risk of belated disapproval by the FDA.

Unfortunately, this approach is not well known throughout the pharmaceutical and biotechnology industries and is currently underutilized.

Implementation Plan:

NCI will develop and implement a communication campaign to enhance industry awareness of this expedited process. NCI will consult with FDA to identify any changes in agency guidelines or other documentation that would increase awareness, and will work with industry to identify outreach mechanisms likely to be most productive. Approaches could include special seminars or workshops, perhaps in conjunction with existing scientific meetings, articles in professional publications, printed materials, and one-to-one outreach aimed at clinical research leaders in industry.

Enhancement Initiative 3:

In collaboration with CMS and other payers and stakeholders, establish a robust and transparent process for identifying clinical studies that might have routine and clinical costs supported using traditional reimbursement mechanisms.

Rationale:

It is essential to improve the efficiency not only of the clinical research enterprise but also of the regulatory and reimbursement frameworks within which it operates. Ideally, these interacting processes will become fully synergistic toward the goal of making beneficial new technologies rapidly available and appropriately used.

The pace of clinical evaluation can only match the pace of biomedical discovery if models are developed to conduct large scale, real-time clinical research throughout the health care delivery system. Availability of CMS funds for reimbursement of some well-defined and routine clinical care costs in cancer clinical trials will decrease barriers to patient enrollment, enhance the generalizability of the conclusions, and help make additional studies possible. Working together with other stakeholders, CMS and NCI can identify a portfolio of clinical research studies that are prioritized, designed, and implemented to be responsive to the information needs of decision makers (patients, clinicians, and policymakers). Formal CMS involvement under well-defined rules in collaboration with NCI may encourage industry to invest in additional clinical studies that can leverage these benefits.

CMS-NCI collaboration can increase the number of studies designed with questions of routine practice in mind, and can increase the speed with which critical reimbursement decisions are made and effective new therapies enter broad clinical practice.

Implementation Plan:

CMS-NCI discussions are ongoing with respect to Medicare reimbursement for the costs of routine and investigational clinical costs in nine specific NCI-supported trials exploring off-label drug treatments for colorectal cancer and with respect to possible coverage for fluorodeoxyglucose-positron emission tomography (FDG-PET) in cancer care in the context of well-designed prospective clinical studies. CMS and NCI are also currently in discussions concerning specific activities to develop a generalizable conceptual framework for identifying studies that may be appropriate candidates for "coverage with evidence development" and to create study designs that address both CMS and NCI objectives. Discussions are also ongoing concerning mechanisms for engagement of stakeholders and payers beyond CMS to establish processes for identifying and prioritizing studies that are appropriate targets for collaboration.

Prioritization/Scientific Quality Initiatives

Introduction:

Enhanced scientific quality and prioritization of clinical trials is potentially the most important goal for the redesigned NCI clinical trials enterprise. The need for efficient use of resources and the urgency of making new therapies available to patients requires that NCI sponsor the best-designed trials, addressing the most important questions, leveraging the most significant scientific advances. Achieving this goal requires that design and prioritization of clinical trials be improved and that the tools of molecular medicine and other correlates of clinical response be applied in a timely, prioritized, and high quality manner to enhance clinical trial outcomes.

Clinical trial design and prioritization can be enhanced in several ways. The first is by a proactive examination of strategic directions for both early phase drug development trials and later stage studies designed to demonstrate efficacy for disease-specific management. The second is to establish an open, collaborative process for encouraging innovation, evaluating new ideas, and designing clinical trials that are not only based on the best science but are also attractive to patients and practicing oncologists. The third is to develop an efficient prioritization system that involves the broad oncology community in allocating available resources to support the most important clinical trials and reduce duplication and overlap.

Each of these enhancements depends on greater cooperation between the NCI and academic researchers, community oncologists, patient advocates, other federal agencies, and industry. The result will be a more open and transparent process for the design, prioritization, and conduct of clinical trials that are both science-driven and meet the needs of patient care.

Correlative science and quality of life studies have great potential to improve the value of clinical trials and can be integral to the design of a trial. However, current funding mechanisms and prioritization processes do not allow such studies to be initiated in a timely fashion so that they are optimally coordinated with the conduct of a clinical trial. An approach needs to be developed to integrate the funding and prioritization of these studies within the overall clinical trial prioritization process.

To achieve the goals of more effective clinical trial design and prioritization, including integration of correlative science and quality of life (or outcome) studies, the CTWG proposes six new initiatives. Once the proposed prioritization system has been successfully implemented for studies of new therapies, expansion to include studies of new preventive agents will be investigated.

New Initiatives:

1. Establish an Investigational Drug Steering Committee to collaborate with NCI in the design and prioritization of early phase drug development trials with agents for which CTEP holds an IND.

2. Establish a network of Scientific Steering Committees to address the design and prioritization of phase III trials that leverages current Intergroup, Cooperative Group, SPORE, and Cancer Center structures and involves the broad oncology community.

3. Enhance patient advocate and community oncologist involvement in clinical trial design and prioritization through representation on Steering Committees and creation of patient advocate and community oncologist focus groups.

4. Establish a funding mechanism and prioritization process to ensure that the most important correlative science and quality of life studies can be initiated in a timely manner in association with clinical trials.

5. Establish a process for ensuring that correlative science studies conducted in association with clinical trials are performed according to standard protocols and standardized laboratory practices.

6. Develop a plan for integrating prioritization of all phase II trials performed by Cooperative Groups, SPOREs, Cancer Centers, and P01, R01 and NCI intramural investigators into the processes established by the Investigational Drug Steering Committee and the Scientific Steering Committees.

New Initiative 1:

Establish an Investigational Drug Steering Committee to collaborate with NCI in the design and prioritization of early phase drug development trials for which CTEP holds an IND.

Rationale:

The proposed Investigational Drug Steering Committee (IDSC) is designed to provide NCI with broad external scientific and clinical input for the design and prioritization of phase I and phase II trials with agents for which CTEP holds an IND. The goals of the IDSC are to enhance strategic input, increase the transparency and openness of the trial design and prioritization process, achieve optimal phase I and phase II trial designs for the most promising agents and, ultimately, increase the predictive value of early phase trials, resulting in the design of more successful phase III trials.

Implementation Plan:

Membership

The IDSC will include the Principal Investigators of phase I U01 grants and phase II N01 contracts, several senior CTEP staff members or their designees, and additional representatives with expertise in biostatistics, non-oncologic clinical trial and drug development methodologies, correlative science technologies, radiation oncology, etc., as well as patient advocates and community oncologists, as needed. Experts in specific molecular markers will be included as ad hoc members for consideration of specific agents.

Responsibilities

Strategic Input. In association with the semi-annual CTEP Investigational Drug Branch meetings, the IDSC will organize open, structured discussions of scientific and clinical strategic directions in drug development. The discussions will focus on critical new questions for early stage clinical trials, including emerging technologies, gaps in the drug development pipeline, new therapeutic opportunities, correlative science strategies, and advances in clinical trial methodology. Based on these discussions, the IDSC will provide input to CTEP regarding future scientific and clinical strategic directions.

Clinical Development Plans. Prior to Letter of Intent (LOI) solicitation, the IDSC will provide input regarding Clinical Development Plans prepared by CTEP staff for all new drugs and selected current drugs. As Clinical Development Plans evolve over time, the IDSC will provide continued input.

Strategic LOI Evaluation. Periodically the IDSC will assess, from a strategic perspective, CTEP-approved LOIs as well as unsolicited LOIs that were rejected to determine whether the Clinical Development Plan for an agent should be modified. When requested by CTEP, the IDSC will provide input on unsolicited LOI's to assist in CTEP decision-making.

Expert Opinion. When requested, the IDSC will address specific scientific and/or clinical questions with regard to early stage clinical trials, provide input to the NCI Drug Development Group[1] concerning a decision to move a specific agent into clinical development, and provide input regarding the resolution of investigator appeals of CTEP LOI decisions.

[1] The NCI Drug Development Group is responsible for prioritizing use of NCI resources for preclinical and clinical development of new agents.

New Initiative 2:

Establish a network of Scientific Steering Committees to address design and prioritization of phase III trials that leverages current Intergroup, Cooperative Group, SPORE, and Cancer Center structures and involves the broad oncology community.

Rationale:

The proposed prioritization system for phase III trials is designed to promote an open, collaborative process for setting clinical trial priorities and reducing trial duplication and overlap. The goals of this system are to ensure a well-informed evaluation of strategic directions; to coordinate and integrate the best ideas arising from Cooperative Groups, Cancer Centers, SPOREs, P01s, R01s, Community Clinical Oncology Programs (CCOPs), and NCI intramural investigators; and to stimulate greater involvement by practicing oncologists, patient advocates, and NCI staff early in the process of trial design and prioritization. The result should be more rapid and cost-effective development of successful new therapies due to an efficient prioritization process that is closely integrated with both the established Cooperative Group clinical trial implementation system and the translational clinical research activities currently conducted by Cancer Center, SPORE, P01, R01, and NCI intramural investigators.

Implementation Plan:

Overall Approach

The proposed implementation plan is designed to leverage existing Intergroup, Cooperative Group, SPORE, and Cancer Center structures by creating Scientific Steering Committees for each major disease area as well as for pediatric oncology and symptom management/supportive care. All phase III concepts and protocols funded by NCI, regardless of mechanism (i.e., Cooperative Group, SPORE, Cancer Center, P01, etc.), will be prioritized through this process. Implementation will be staggered with the process being implemented for a limited number of diseases in the first two years. Since this represents a significant restructuring of the process for selecting phase III trials, a formal evaluation will be conducted two years after the process has been implemented for the initial disease categories. If the initial implementation is judged successful, the process will be extended to most diseases within four years.

The proposed prioritization process differs in important respects from the Concept Evaluation Panels established in response to the 1997 Armitage Report. The Concept

Evaluation Panels functioned as an arms-length external peer review process for phase III concepts proposed by the Cooperative Groups. The process was designed to ensure that the studies were of high scientific and clinical merit, and focused on the evaluation of fully developed concepts for phase III studies. The Panels were not organized to develop and refine a concept from an elemental stage, based on an open and collaborative sharing of ideas among peers. The Scientific Steering Committees, in contrast, are designed not only to provide robust peer review of proposed concepts, but also to facilitate the sharing of ideas among a broad range of clinical investigators, basic and translational scientists, NCI staff, community oncologists and patient advocates in the development of those concepts. The result should be scientifically rigorous phase III concepts that have been optimized through the collaborative effort and expertise of an extramural clinical trials community empowered to create the best-designed trials asking the most important questions.

Scientific Steering Committees

The Scientific Steering Committees will replace the existing Intergroup structures and serve to rationalize and facilitate a large number of current meetings and other formal and informal interactions that occur in the context of Cooperative Groups, Cancer Centers, SPOREs, P01s, etc. These existing interactions often involve clinical investigators, basic and translational scientists, community oncologists, patient advocates and NCI staff but, because of fragmentation and overlap, they may fail to provide an effective forum for setting priorities. In contrast, the Scientific Steering Committees will provide an organized, inclusive, and open forum for consideration of new ideas in the context of evolving scientific and clinical priorities, and the opportunity for integration of those ideas into more robust phase III trials. The importance and value of this approach is demonstrated by recent initiatives from the Gastrointestinal Intergroup to establish similar structures to guide new ideas and scientific advances efficiently into phase III trial designs. Although the initial Scientific Steering Committee organization is around disease sites, the prioritization system could evolve, if appropriate, to focus around specific molecular targets or therapeutic approaches.

Membership. Each Scientific Steering Committee will have approximately 8-20 members with size correlated with the number of phase III concepts likely to be developed.

1. Membership will include Cooperative Group Disease Committee Chairs and clinical, basic, and translational investigators from Cooperative Groups, CCOPs, SPOREs, P01s, R01s, Cancer Centers, and the NCI intramural program who are experts in the relevant disease. The Pediatric Oncology Committee will include members of the Children's Oncology Group, the Pediatric Brain Tumor Consortium and other pediatric oncology investigators, and the Symptom Management Committee will include several CCOP representatives.
2. All Scientific Steering Committees will have at least one community oncologist and one patient advocate. If the group is large, additional community oncologists and patient advocates will be appointed. Community oncologist representatives

will be investigators from CCOPs or Cooperative Group affiliates and will have significant experience treating the target disease.

3. NCI staff members will include the Clinical Investigations Branch staff member responsible for the disease category, the Branch Chief and a biostatistician from the Biostatistics Research Branch. Other NCI staff such as members of the Investigational Drug Branch, the Cancer Diagnosis Program, the Radiation Oncology Sciences Program, and the Cancer Imaging Program will be included as ad hoc members for consideration of specific concepts.
4. Appropriate correlative science and quality of life experts will be included as ad hoc members for consideration of specific concepts.
5. As appropriate for specific agents, representatives from industry, CMS, and/or the Investigational Drug Steering Committee (or other experts in early therapeutics development) will be invited to participate.

Responsibilities.

1. The Scientific Steering Committees will organize periodic, invited State-of-the-Science Meetings to identify critical questions and unmet needs, to prioritize key strategies and future concepts to test, and to facilitate innovation. Meetings will be informal and confidential to encourage discussion of newly-breaking results and ideas and to facilitate brainstorming. Attendees will include a broad range of clinical, basic, and translational investigators whose work is relevant to the specific disease as well as community oncologists and other oncology health care providers, patient advocates, and senior strategic thinkers from throughout oncology. Status and results of selected phase II trials would be a special feature at each meeting. Based on these meetings, the Committees will disseminate key strategic priorities for future trials to the relevant oncology communities.
2. The Scientific Steering Committees will develop phase III concepts from an elemental stage, as well as evaluate and refine ideas for phase III trials developed by Cooperative Group Disease Committees or investigators from Cancer Centers, SPOREs, P01s, etc. Based on these deliberations, the Committee will recommend which concepts should proceed to the protocol stage.
3. Concepts recommended by the Scientific Steering Committees will be submitted to NCI through the lead Cooperative Group for that concept. If the concept originated outside the Cooperative Group structure, the originating investigator will be the Principal Investigator (PI) and a Cooperative Group investigator will be a co-PI on the protocol.
4. Given the active participation of NCI staff throughout Committee deliberations, it is expected that the majority of concepts will be reviewed by an expedited process. If Committee deliberations indicate significant scientific or clinical concerns about the concept, NCI could conduct a formal scientific quality review. NCI will review all concepts recommended by the various Committees from a broad programmatic and budget perspective including prioritization across diseases.
5. Once the concept is approved by NCI, a protocol will be prepared by the lead Cooperative Group for submission to NCI. The Scientific Steering Committee will receive the final protocol for comment before NCI provides its approval.

6. The Scientific Steering Committees will monitor implementation of national phase III trials through the Cooperative Group and Cancer Trials Support Unit (CTSU) structures and periodically evaluate trial status in terms of accrual, unforeseen implementation issues, etc.

New Initiative 3:

Enhance patient advocate and community oncologist involvement in clinical trial design and prioritization through representation on Steering Committees and creation of patient advocate and community oncologist focus groups.

Rationale:

The current process for design and prioritization of NCI-funded clinical trials involves a certain degree of participation by community oncologists and patient advocates. However, their participation is by no means uniform. Enhancing the involvement of community oncologists and patient advocates has several potential benefits. It will facilitate the development of clinical protocols that are attractive for patient enrollment and are feasible in the community setting. It will also promote development of trial designs that address the questions facing patients and physicians when making treatment decisions. Ultimately, it will result in the development of new therapies that are useful and practical for patients and their treating oncologists and have outcomes that improve patient care.

Implementation Plan:

Representation on Scientific Steering Committees

Each Scientific Steering Committee will have at least one community oncologist and one patient advocate member in attendance at each meeting. If the Committee is large, additional community oncologists and patient advocates will be appointed to maintain adequate representation.

Focus Groups

1. Each Scientific Steering Committee will convene periodic patient and community oncologist focus groups to solicit general input and promote efficient trial accrual. For orphan diseases, a combined focus group will be convened. It is expected that these focus groups will also serve as a source for future members of the Scientific Steering Committees.

2. Focus group agendas will include topics such as current treatment issues facing patients and community physicians, important treatment questions that potentially could be answered by trials, clinical trial designs currently under consideration, and future trial designs proposed to answer new questions.

3. If recommended by a patient advocate, community oncologist or other Scientific Steering Committee member, the Committee will ask focus group members to provide broader input to the design of a specific trial. Based on the relationships and knowledge gained from the annual meetings, this feedback can be provided in a timely fashion so as to not delay decision-making.

Community Oncologist/Patient Advocate Steering Committees

Two Steering Committees will be established, one for community oncologists and one for patient advocates, to provide input regarding the involvement of these constituencies in the NCI clinical trials enterprise. Each Steering Committee will meet annually to address policy issues across diseases, share best practices, and identify areas for improvement. Membership will include the community oncologists and patient advocates on the Scientific Steering Committees and, as needed, additional representatives from CCOPs and patient advocacy organizations.

New Initiative 4:

Establish a funding mechanism and prioritization process to ensure that the most important correlative science and quality of life studies can be initiated in a timely manner in association with clinical trials.

Rationale:

Realizing the promise of molecular medicine will require that high quality correlative science studies be conducted in association with clinical trials, especially multisite phase III trials designed to establish clinical efficacy. However, the current mechanism for funding phase III trials does not readily provide for such correlative studies. Therefore, these studies have generally been supported through submission of a separate funding request. This is inefficient both in terms of timing relative to the conduct of the trial, and because a typical Study Section review is not structured to take into account the importance of the study in the context of the broader clinical trials prioritization process. The result is that many correlative science studies that could improve patient care are not being performed effectively today due to lack of funding. In addition, clinical trials of new agents that may be very effective in subsets of patients are often unsuccessful because the diagnostic/predictive tests that could identify those patients have not been evaluated in the context of a phase III study. There is also no efficient process for prioritizing and funding quality of life studies associated with phase III trials.

Although funds for correlative science and quality of life studies could be added to the Cooperative Group budgets, this may not be the best approach. The value of these studies is very trial-specific and a general allocation to all Cooperative Groups may not result in an optimal distribution of funds. Moreover, although some funding is available through existing CTEP, SPORE, Cancer Center, or R01/P01 sources for correlative studies associated with phase II trials, these funds are usually limited to a specific site, laboratory, or investigator.

Therefore, it is proposed that a separate NCI budget be created and a prioritization process developed to expeditiously fund correlative science and quality of life studies associated with NCI-supported clinical trials. This prioritization will be closely integrated with the new clinical trials prioritization process described above. The goals are to fund the most important correlative science and quality of life studies, to ensure that clinical trial expenditures are optimized through collection of important correlative science data, and to avoid the delays associated with applying for traditional grant funding.

Implementation Plan:

Budget

NCI will establish a separate budget to fund correlative science and quality of life studies conducted in association with NCI-funded clinical trials. The proposed mechanism will involve creation of a pool of funds that will be allocated by NCI based on recommendations from the Steering Committees and the appropriate NCI Divisions, and reviewed by the Clinical Trials Oversight Subcommittee of the NCAB. NCI will earmark specific portions of the budget for quality of life and correlative science studies, respectively.

Eligible Studies

Phase III Trials. The primary purpose of this budget is to fund studies in association with phase III trials when the cost of the studies is too large to be covered by Cooperative Group or other NCI support mechanisms in a sufficiently timely manner. Studies integral to the design of a clinical trial (e.g. an entry criterion) or studies that must be conducted in real time for the success of the trial will be especially important to support.

Phase I and Phase II Trials. Studies conducted in association with phase I and phase II trials funded through CTEP, Cooperative Group, Cancer Center, SPORE, P01, R01, and other grant mechanisms will be eligible if the proposed studies are beyond the scope of the original grant or contract.

Prioritization

Prioritization Criteria. NCI will convene a group of external experts in clinical research, biostatistics, bioinformatics, pathology, imaging, translational and correlative science and quality of life to assist in establishing the criteria for prioritizing study proposals. In addition to scientific quality, the criteria might include expected clinical impact, importance of studies to the overall value of the trial, cost-effectiveness, degree of innovation, availability of other funds, etc. NCI will apply these criteria when deciding which of the studies proposed by the Scientific Steering Committees and NCI Divisions should receive supplemental funding. The criteria will be updated periodically.

Phase III Trials. Studies associated with phase III trials will be proposed for funding by the appropriate Scientific Steering Committee. For concepts containing a significant correlative science or quality of life component, the relevant Scientific Steering Committee will involve appropriate subject matter experts (e.g. pathology, imaging, comprehensive molecular analysis, immunohistochemistry, quality of life, etc.) in all deliberations concerning the concept. For trials where the correlative science is integral to the trial design (e.g. as an entry criterion), the scientific quality and impact of the correlative science study will be critical in reaching a decision to recommend the overall trial concept. If the study is not integral to the trial, the Committee will provide a separate review of the quality and importance of the correlative science or quality of life study for consideration by NCI when deciding on the priority for funding.

Phase I and Phase II Trials. Correlative science and quality of life studies associated with phase II trials conducted under Cooperative Group, Cancer Center, SPORE, P01, R01 or N01 mechanisms and phase I trials conducted under the U01 mechanism will be proposed for supplemental funding by the relevant NCI program staff based on scientific quality of the study and its importance to the value of the trial.

Funding Decisions. Based on the proposals from the Scientific Steering Committees and NCI Divisions, NCI will present a priority list of studies recommended for funding to the NCAB Clinical Trials Oversight Subcommittee (see Enterprise-Wide Initiative 1 on page 50) for review and approval.

Additional Funding Sources for Approved Studies

Industry. For studies that have the potential to increase the market for a drug, biologic, or diagnostic product produced by industry, the Principal Investigator and NCI will work cooperatively to negotiate full or partial industry support for the proposed study.

CMS/Other Payers. If a correlative science study has the potential to reduce the overall cost of patient care for a specific disease category, NCI will share details of the study with CMS and other payers and seek to negotiate reimbursement for the cost of the correlative studies.

New Initiative 5:

Establish a process for ensuring that correlative science studies conducted in association with clinical trials are performed according to standard protocols and standardized laboratory practices.

Rationale:

In the era of evolving molecular diagnostics and targeted therapeutics, biomarkers[2] will increasingly be used as predictive and prognostic markers to guide therapy decisions and as novel endpoints to assess drug effects and predict clinical benefit. Establishing standards for the measurement, analysis, and reporting of biomarker data will be essential for obtaining the robust correlative science information necessary to fully evaluate new targeted disease therapies. Such measurement standards will increase the ability to compare data across trials and laboratories, facilitate comparisons of large data sets from multiple trials, and reduce duplication in defining assay methods and data requirements. Moreover, such standards will be essential if data are to be submitted to the FDA in support of a label indication.

Implementation Plan:

Overall Approach

NCI will develop a process for establishing standards for laboratory assays and imaging procedures used in correlative science studies for NCI-funded clinical trials. This process will involve experts in each of the applicable technologies including imaging, comprehensive molecular analysis, pathology, immunohistochemistry, etc. as well as representatives from National Institute of Standards and Technology (NIST) and industry.

Defining Technology Categories for Standards

The first task will be to determine which technology categories are appropriate for establishment of standards and which technologies need further development and refinement before meaningful standards can be elaborated.

Standards Documents

If establishment of standards is appropriate for a given technology, a document will be developed outlining the standards that should be met for the laboratory assay or imaging procedure in the context of specific types of clinical trials. This will include both

[2] The term biomarker as used here conforms to the FDA definition of biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." Although a biomarker can serve as a surrogate endpoint, the terms are not synonymous.

procedure-specific standards (e.g., interval between contrast agent injection and scan, temperature for specimen processing, etc.) as well as standards for quality control, validation, documentation, etc. If established mechanisms for accreditation or standards setting exist for a particular technology [e.g., Clinical Laboratory Improvement Amendments (CLIA), College of American Pathology (CAP), etc.], adherence to those standards will be recommended.

Annual Review and Update

At least annually, NCI will evaluate potential changes in existing standards documents and determine whether additional technologies have advanced sufficiently to make development of standards and issuance of standards documents appropriate.

Registry of Laboratories/Imaging Cores Meeting Required Standards

The NCI will examine the cost and benefits of establishing a registry of laboratories and/or imaging cores in support of clinical trials that meet the required standards for a given technology.

Adherence to Standards

Dissemination. NCI will disseminate to the oncology, pathology, and imaging communities clinical trial biomarker standards developed for particular technologies.

NCI Study Requirements. Correlative science studies in the clinical setting using laboratory or imaging markers or techniques for which standards are established must adhere to those standards or present a compelling justification for deviating from such standards. For studies using novel laboratory or imaging markers or techniques for which standards do not yet exist, the study proposal must provide a set of standards to be used in that trial, and explain the rationale or basis for the selected standards.

Validated Endpoints

NCI will continue to work with the FDA and industry through the Interagency Oncology Task Force to define the relevant issues and establish policies and procedures for validating critical drug development endpoints based on biomarkers.

New Initiative 6:

Develop a plan for integrating prioritization of phase II trials performed by Cooperative Groups, SPOREs, Cancer Centers, and P01, R01 and intramural investigators into the systems established by the Investigational Drug Steering Committee and the Scientific Steering Committees.

Rationale:

The ultimate goal is to coordinate prioritization of all clinical trials funded by NCI. Once a prioritization system is in place for phase III trials and early phase trials with CTEP agents, NCI will investigate whether it is appropriate and feasible to integrate into this system the prioritization of phase II trials performed by Cooperative Groups, SPOREs, Cancer Centers, and P01, R01 and intramural investigators. If such integration is pursued, it will be essential to retain the incentives for innovation and the healthy competition inherent in the current system. Investigator-initiated exploratory phase II trials remain the discovery engine that will ultimately drive change. Nevertheless, the clinical trials enterprise will function more effectively if these new ideas are shared and coordinated with the strong systems in place for moving those ideas forward toward clinical practice.

Implementation Plan:

Enhanced Communication

The first step will be involvement of investigators conducting exploratory phase II trials in the activities of the Scientific Steering Committees. Reports on status and results of selected phase II trials will be a special feature at each State-of-the-Science Meeting.

Enhanced Information Sharing

As the comprehensive clinical trials database is implemented, information on these exploratory trials will be included to facilitate communication and avoid duplication. Such information sharing would also alert investigators to opportunities for combining small trials asking related questions into larger, more broadly meaningful trials.

Coordinated Prioritization

Achieving this goal will have two important prerequisites. The first is restructuring of the NCI approval and funding process so that exploratory phase II trials can be integrated into a comprehensive prioritization system. The second will be to develop prioritization criteria that result in increased efficiency and coordination without adversely affecting innovation. These criteria are likely to be different from the criteria used for prioritizing phase III trials or CTEP investigational drug trials. Therefore, as the prioritization process for phase III trials and early phase trials with CTEP agents is being implemented, NCI will assess whether integration of these early stage trials into a comprehensive NCI clinical trials prioritization system would be valuable and, if so, how such integration might be accomplished. This assessment will be performed in concert with the phase II investigator community who will then be involved in developing an implementation plan, if appropriate.

Standardization Initiatives

Introduction:

Transformation of the cancer clinical trials system into an efficient enterprise that produces quality results in a timely fashion hinges on establishing enterprise-wide standardization of several important tools and procedures. Creating an interoperable information technology platform would facilitate the reporting, analysis, and sharing of data across sites and promote team science. Developing commonly accepted Common Data Elements and standard Case Report Forms would reduce data requirements and the need for investigative sites to manage a wide array of different forms and data entry processes. Instituting a widely recognized credentialing system for research personnel and sites would eliminate the need to reestablish credentials each time a trial is initiated, further assisting both trial sponsors and investigative sites. Significant time savings would also be achieved by adopting standard contract language that minimizes the need for recurrent intellectual property, confidentiality, and other negotiations before each clinical trial contract is signed.

Standardization in each of these key areas will speed the initiation and conduct of clinical trials, minimize duplication, and ultimately result in a faster, more efficient clinical trials system. To achieve this improved standardization, the CTWG proposes four initiatives; three of these are new, and one proposes to significantly enhance current NCI activities.

New Initiatives:

1. Promote establishment of national clinical trial information technology infrastructures that are fully interoperable with NCI's cancer Bioinformatics Grid.

2. Achieve industry and FDA concurrence on standard Case Report Forms incorporating Common Data Elements.

3. Develop a credentialing system for investigators and sites that is recognized and accepted by NCI, industry sponsors, clinical investigators, and clinical trial sites.

Enhancement Initiative:

1. Establish commonly accepted clauses for clinical trial contracts.

New Initiative 1:

Promote establishment of national clinical trial information technology infrastructures that are fully interoperable with NCI's cancer Bioinformatics Grid.

Rationale:

The universal acceptance of shared standards for collection, management, and sharing of cancer clinical trial data would be of enormous benefit in terms of cost-effectiveness and comparability of results across trials and sites. Such standards would facilitate the development and deployment of modular information management applications that are interoperable among the various research stakeholders. They would also permit integration of the clinical research infrastructure into emerging standard electronic health record systems.

NCI's caBIG initiative, through its Clinical Trials Management Systems workspace, and in partnership with international standards-developing organizations (HL7, CDISC) is developing a comprehensive collection of standards and standards-based tools covering the entire clinical trial life-cycle. These tools can be available for adoption as web-accessible solutions interfaced with existing information technology (IT) infrastructures, or can be coupled with existing commercial software and deployed as an entire system for sites that lack a robust clinical trials IT architecture. The long-term goal is for all clinical trial sites either to migrate to the caBIG architecture or to develop interfaces and other required enhancements such that their IT architecture is fully interoperable with the caBIG standards-based architecture.

Implementation Plan:

The CTWG endorses the universal adoption and deployment of a common, standards-based IT infrastructure for the management of clinical trials across the NCI-supported cancer enterprise that is fully interoperable with the caBIG architecture.

Increase Clinical Investigator Input into caBIG Development

Membership in caBIG's Clinical Trials Management System Workspace will be expanded to include additional clinical investigators from Cancer Centers, Cooperative Groups, CCOPs, SPORES, P01s, etc. This broader representation and commitment of the clinical investigator community will improve the link between the caBIG development teams and clinical investigators to ensure that tools developed with caBIG standards are fully responsive to the needs of clinical researchers. Moreover, enhanced clinical investigator involvement will facilitate caBIG understanding and support from the clinical investigator community.

Harmonization of Internal NCI IT Systems

NCI will establish a timeline for harmonizing all internal NCI IT systems [i.e., CDUS, the Clinical Trials Monitoring Service (CTMS), CTSU, Adverse Event Expedited Reporting System (AdEERS), etc.] with caBIG standards.

Interoperability Requirements

caBIG has issued guidelines outlining the requirements necessary for a system to be caBIG-compliant. The caBIG management team will work with Cooperative Groups, SPOREs, Cancer Centers, etc., to determine the approach, timeline, and resources necessary for either adopting the caBIG IT systems, or making current IT systems interoperable with caBIG. caBIG will also assist in providing resources necessary for effecting caBIG interoperability. NCI will require that all sites conducting NCI-supported clinical trials outside the CTSU provide, by a to-be-determined deadline, a plan to become caBIG-compatible. NCI award guidelines will be modified to require a plan for moving to caBIG interoperability, and new RFAs/RFPs requiring informatics support will be reviewed for caBIG compatibility.

Web-Based Trial Initiation Tool

caBIG will develop and make available a web-based trial initiation portal to facilitate protocol activation at sites. This web-based tool will be a caBIG core module so any investigator can easily use it to start up phase III treatment and complex phase II trials. The tool will provide a schema and checklist that reminds sites of staff and services that must be in place to successfully implement a trial (e.g., personnel requirements, necessary infrastructure, IRB submission requirements, data management needs, procedure instructions, etc.). The content will be similar to the trial initiation materials provided to sites by industry sponsors. A contractor will be retained to define the content for the trial initiation tool, and caBIG will generate the required templates and make the tool available to end-users through a web-based interface.

New Initiative 2:

Achieve industry and FDA concurrence on standard Case Report Forms incorporating Common Data Elements.

Rationale:

Establishing agreed upon standards for the Common Data Elements (CDEs) that should be captured for each trial, the vocabulary in which they are expressed, and common Case Report Form (CRF) templates for collecting them will reduce the effort, time, and cost of initiating and executing trials, minimize duplication of effort, enhance investigators'

ability to compare and analyze data across trials, and facilitate regulatory review. A standard CRF would eliminate the need to generate or regenerate data collection instruments, and the need to constantly re-train staff on their use. CRFs based on CDEs that utilize standard, controlled vocabularies and that are derived from standard information models such as HL7/CDISC will make it easier to share structured data electronically, improve information sharing among cancer researchers, and help to accelerate scientific progress. Agreement on common CRFs would also ensure that only the data required for a given trial is actually collected, which should reduce data requirements.

Implementation Plan:

Harmonize and Expand the Library of Existing CRFs

NCI currently has several sets of standard phase III CRFs and is developing CRFs for phase II trials. Industry has preferred CRFs, which may vary from sponsor to sponsor. While continuing the development of its own CRF repository in collaboration with the clinical research community, NCI will convene a series of meetings with key stakeholders including industry sponsors and FDA representatives to review the current library of NCI and industry CRFs. The goal of this series of meetings will be to develop, with input from a wide audience of stakeholders, a set of harmonized CRFs that include core modules integrating CDEs expressed in standard vocabularies. In order to facilitate regulatory review, FDA involvement will be solicited at the start of the development process. Active industry participation will ensure that industry-specific needs are addressed so that the final set of standard CRFs have the potential to be widely adopted by both the private and public sector research communities.

Implementation and Dissemination

The core library of standard CRFs developed by stakeholder consensus will be accessible through caBIG for unrestricted use by the entire oncology community.

Review and Update

Following development of the standard CRFs, NCI, in collaboration with clinical investigators, industry, and the FDA, will conduct an annual review to determine whether changes are needed in the CDE modules or the existing CRFs, and whether additional standard CRFs should be established for other trial categories.

New Initiative 3:

Develop a credentialing system for investigators and sites that is recognized and accepted by NCI, industry sponsors, clinical investigators and clinical trial sites.

Rationale:

The absence of an officially accepted system for credentialing clinical investigators, research personnel, and research sites results in a redundant system where each sponsor has to re-establish credentials every time a new trial is initiated, even if the investigator and/or site have already been credentialed by the same sponsor. A universal registry of credentialed investigators and sites would speed trial initiation while facilitating rapid communication of new regulations and changes to the clinical research community, and changes in the status of individual investigators and sites to sponsors. Creating a credentialing process and registry will result in cost savings for industry sponsors and clinical sites by simplifying the trial initiation process, and will help keep the investigative community abreast of new trends in clinical trials, including legal, safety, and regulatory changes.

Implementation Plan:

Overall Approach

NCI will partner with relevant professional societies and trade associations [e.g., the American Society of Clinical Oncology (ASCO), the American Association for Cancer Research (AACR), the American Association of Cancer Institutes (AACI), the Oncology Nursing Society (ONS), the Society of Clinical Research Associates (SoCRA), the Association of Clinical Research Professionals (ACRP), the Pharmaceutical Research and Manufacturing Association (PhRMA), the Biotechnology Industry Organization (BIO), etc.] to create a credentialing system and registry for cancer investigators and sites. As appropriate, links to the clinical investigator community outside of cancer research should be pursued to share commonalities among credentialing criteria for research personnel.

Credentialing Criteria

NCI will form a task force composed of NCI staff and staff from interested professional societies and trade associations to define and establish credentialing criteria. The task force will also include representatives from FDA and industry, as well as clinical investigators and other health care professionals from the academic and community oncologist clinical research communities. The criteria for investigators, in addition to information currently collected for the 1572 form, could include the number of new

patients evaluated per year, number of patients enrolled onto clinical trials per year, Good Clinical Practice (GCP) training and experience, investigator biosketch, etc. Investigators will be required to keep their credentials up-to-date, and comply with any changes in the credentialing criteria. The criteria for sites might include staffing ratios and training, IT infrastructure, investigational drug pharmacy facilities and staffing, clinical trial and adverse event monitoring capabilities, IRB functionality, clinical trial volume, and clinical care facilities, among others.

Credentialing System

An NCI/professional society/trade association partnership will be established to develop a formal investigator and site credentialing system for oncology clinical trials, based on the criteria established by the task force. This system should incorporate information from professional organizations that provide certification or training programs to nurses, clinical research associates, pharmacists, etc., such as the ONS, SoCRA, ACRP, and others. The credentialing system will harmonize the data from all such professional societies.

Registry

The same NCI/professional society/trade association partnership will establish and maintain a database of credentialed investigators, information on credentialing of ancillary staff, and credentialed trial sites. As appropriate, NCI will integrate the registry with ongoing efforts of the Federal Investigator Registry of Biomedical Informatics Research Data (FIReBIRD) initiative. Once the database is available, the partnership will promote its use by oncology clinical trial sponsors.

Enhancement Initiative 1:

Establish commonly accepted clauses for clinical trial contracts.

Rationale:

Lack of standard contract language contributes to delays in the startup of clinical trials. Most academic medical centers negotiate a new contract for each new trial that is initiated, even though most of the issues addressed are common across trials and sponsors. This duplication creates large inefficiencies in the system, both in terms of time requirements, manpower needs, direct costs, and opportunity costs. Accepted standards for clinical trial contract language may help reduce the time and effort expended on this aspect of trial startup.

Implementation Plan:

A core set of modular contract templates will be developed that can be adapted easily to a particular trial, that meet a high proportion of contractual requirements governing clinical trials, and that will be acceptable to both NCI and industry sponsors.

NCI/Academia/Industry Conference

NCI will convene a conference of legal and business representatives from industry sponsors, Cancer Centers, other academic institutions, and NCI staff to discuss existing contract clauses developed by NCI, and to determine what is needed to create acceptable language for modular contract clauses that can be used in all trial contracts. Such modular clauses would address intellectual property and licensing, publishing rights, confidentiality of data, risk and indemnification, etc.

Standard Contract Task Force

NCI will establish a task force to develop the concepts generated by the conference into standard modular clauses and templates. A limited number of modular contract templates should be developed that can be selected by industry sponsors, academia, and NCI. The task force will include legal and business representatives from NCI, Cancer Centers, other academic institutions and industry. Obtaining industry endorsement is crucial to the success of this initiative.

Promote Use of Current Templates

Until standard clauses are developed, NCI will promote the use of the current NCI standard contract clauses through posting to the NCI website to improve awareness and increase their utilization.

Operational Efficiency Initiatives

Introduction:

Improving operational efficiency is essential for the cancer clinical trials system to fulfill its promise to deliver new treatments to patients more quickly. There are two critical areas in which operational efficiency could be enhanced. The first is to increase the rate of patient accrual so that trials can be completed in a more timely fashion. The second is to identify and reduce institutional barriers that prolong the time from concept approval to opening of patient accrual at sites.

Opportunities for increasing the rate of patient accrual include aligning NCI funding more closely with the actual cost of conducting a trial, incentivizing high accruing, cost-efficient sites, educating patients and the public about the benefits of clinical trials, and improving the availability of trials to minority populations. Reducing the time required to start trials will require a systematic analysis of the institutional barriers that delay trial initiation and a reduction in current regulatory burdens.

To achieve improved operational efficiency in each of these areas, the CTWG proposes the following five initiatives, two of which are new, and three that represent efforts to significantly improve current approaches.

New Initiatives:

1. Restructure the funding model for phase III efficacy trials to incentivize more rapid rates of patient accrual.

2. Identify the institutional barriers that prolong the time from concept approval to the accrual of the first patient, and develop solutions for overcoming these barriers.

Enhancement Initiatives:

1. Promote patient and public awareness and understanding of clinical trials.

2. Expand current outreach programs to increase the recruitment of minority populations to cancer clinical trials.

3. Develop approaches for enhancing adoption of centralized Institutional Review Board processes.

New Initiative 1:

Restructure the funding model for phase III efficacy trials to incentivize more rapid rates of patient accrual.

Rationale:

A complex and expensive infrastructure is required to conduct clinical trials in a manner that ensures proper human subject protection, rigorous scientific design, meticulous data collection, and valid biostatistical evaluation. Past analyses of cancer clinical trials estimated average per-case costs for investigators/sites to be from about $4,000 to about $6,000.[3] However, current per-case reimbursement to sites for most NCI-funded treatment trials is $2,000. This differential between actual clinical trial costs and current NCI reimbursement for patient accrual is not sustainable over the long term for either the Cooperative Groups or for the CCOPs.

However, there may be certain cost inefficiencies in the current system. For example, it is unknown whether current models for statistical, data management, auditing, and administrative support are optimal, whether they are either over- or underfunded, or whether economies of scale might be possible or desirable. In addition, maintaining sites under the Cooperative Group mechanisms that accrue only a few patients per year is costly to the system, because fixed costs for site infrastructure, personnel, personnel training, auditing, and data management must be spread over small numbers of patients, resulting in a high per-case cost. Such sites could be managed more efficiently through the CTSU.

The ultimate goal of this initiative is to increase the rate of patient accrual so that enrollment for clinical studies can be completed more rapidly but in a way that is cost efficient and preserves the funding flexibility of the present system.

Implementation Plan:

Financial Analysis of Phase III Trial Costs

NCI will conduct a comprehensive financial analysis of clinical trial costs, moving beyond published analyses of per-case costs to analyze infrastructure costs in greater detail, including operations and statistical offices, regulatory activities, etc. The goal is to identify areas where Cooperative Groups and CCOPs are not receiving adequate compensation, and at the same time, identify inefficiencies where costs could be reduced.

[3] Emanuel, E., *et al.* The Costs of Conducting Clinical Research, *Journal of Clinical Oncology*, 2003; 21: 4145-50.

An analysis of the cost savings that may be achieved from the closure of low accruing sites will be an integral part of this assessment.

Evaluation of Data Quality as a Function of Patient Accrual Rate

Poor data quality adversely affects not only trial results but also cost-effectiveness because of the expense of the data clean-up that may be required to salvage usable results. NCI will perform an analysis of data quality as a function of patient accrual rate to evaluate the perception that the quality of data obtained from low accruing sites lags behind that of sites with high patient accrual rates. The evaluation will consider not only the absolute rate of patient accrual but also the infrastructure (clinical research associates, nurses, data managers, etc.) available to support a given rate of accrual at a particular site. The analysis should evaluate whether, for a given support infrastructure, a patient accrual threshold exists at which data quality may suffer. The results will help determine criteria for the optimal numbers of patients that can be accrued in the context of a specific clinical trial support infrastructure without compromising data quality.

New Phase III Trial Funding Model

Based on the financial and data quality analyses, NCI will develop a new funding model for patient accrual sites, operations offices, and statistical centers. The model must take into consideration personnel requirements, the number, size and complexity of trials, and follow-up burden. Furthermore, the model may not be a one-size-fits-all solution for all Cooperative Groups and CCOPs and may require modification on a case-by-case basis and a degree of flexibility from year to year. The main goals are to align funding more closely with the actual cost of conducting a trial and to enhance cost-effectiveness. Several recommended principles for this new funding model are described below.

Align Reimbursement with Trial Complexity. Not all trials are alike. Some may require additional follow-up or documentation due to medication side effects, and some may utilize complicated and prolonged therapeutic regimens requiring additional laboratory testing, etc. NCI will develop a process for evaluating trial complexity and investigate establishing a tiered reimbursement schedule that will match reimbursement more closely to the actual cost of running a trial. Such a tiered system will also be reflected in the funding of CCOP grants.

Reduce Duplication of Administrative Functions. NCI will work with the Cooperative Groups to implement economies of scale, such as consolidation of administrative functions and auditing processes, where this is supported by the financial analysis, to reduce duplication and overlap.

Incentivize High Accruing, Cost-Efficient Sites. Clinical trial sites that accrue greater numbers of patients will generally be more cost-efficient. An incentive system to increase the number of high accruing sites and phase out inefficient low accruing sites may thus enhance cost-effectiveness. To that end, NCI will develop a plan to provide

supplements for high accruing sites to help cover infrastructure costs. Since infrastructure requirements increase with patient numbers, NCI will establish a range of supplements that correlate with varying levels of patient accrual. When patient accrual exceeds a certain threshold, a supplemental grant will be provided and the size of the supplement will increase as accrual rises. The financial and data quality analyses described above will assist in setting the appropriate accrual targets for various levels of supplemental funding. Such an approach will cause patient accrual expense to grow as the incentive system moves a higher proportion of accrual to the high accruing sites. However, there should be offsetting benefits in cost efficiency and more rapid trial completion.

Establish Minimum Accrual Standards. Each Cooperative Group will propose minimum standards for patient accrual based on its own site characteristics and obtain NCI approval for that standard. This target is anticipated to be approximately ten to twelve patients per year. If sites fall below their targeted levels for two consecutive years, they will lose their Group membership. As independent sites, they could still access NCI-sponsored trials via the CTSU, where the current minimal accrual standard is five patients per year.

Adjust CCOP Funding for High Accrual Rates. NCI expects CCOPs to accrue high volumes of patients. Therefore, as supplemental funding is provided for high-accruing Cooperative Group sites, a similar increase will be provided for CCOP participants accruing at similar levels, with the increase reflected in the CCOP grant award. Any funding available to Cooperative Group members above and beyond NCI support, such as industry funding to compensate for additional work related to a complex trial, will also be available to CCOP members without compromising their grant funding.

New Initiative 2:

Identify the institutional barriers that prolong the time from concept approval to accrual of the first patient, and develop solutions for overcoming these barriers.

Rationale:

The time required to move from concept approval to accrual of the first patient for NCI-supported clinical trials is lengthy, often in excess of 18 months. Such a long delay impedes clinical progress; at times the clinical question is no longer relevant by the time the trial is started. Although specific barriers to rapid protocol activation have been documented at individual clinical sites, and a substantive reduction in the turnaround time for protocol review by NCI has been achieved, there has been no generalizable systems analysis that would clarify key barriers to starting a trial, and identify changes likely to lead to improvement. In light of the rapidity with which novel treatments for a number of previously-refractory malignancies are becoming available for clinical testing, the need to

understand these barriers and to develop ways to overcome them has never been more urgent.

Implementation Plan:

Academic management experts knowledgeable in evaluating workflows will be engaged to examine the cancer clinical trial startup process operating in real-world settings. The goals are an in-depth understanding of the processes that constrain speedy trial initiation and a clear set of recommendations for relieving the bottlenecks. Such an analysis is ongoing at one major NCI-designated Comprehensive Cancer Center and will be expanded to other NCI-funded sites.

Enhancement Initiative 1:

Promote patient and public awareness and understanding of clinical trials.

Rationale:

Many patients are unaware that they are eligible for clinical trials, and many are unaware of the benefits of clinical trials. To address this need, the NCI has two offices - the Office of Education and Special Initiatives (OESI) and the Office of Communications (OC) - that are actively involved in developing and promoting clinical trial education programs for multiple audiences as well as in providing access to specific types of clinical trials. However, many NCI-funded investigators do not take full advantage of these resources. The CTWG proposes enhanced interaction of OESI and OC staff with patient advocates and clinical investigators to build awareness of clinical trials.

Implementation Plan:

Overall Approach

NCI staff from OESI and OC should become a bridge between NCI clinical investigators and the public to communicate the benefits of oncology clinical trials.

Patient Advocacy Group Outreach

Patient advocacy groups have been identified by patients as providing credible educational information on clinical trials.[4] OC and OESI staff will continue to work actively with the NCI Office of Liaison Activities and the patient advocacy programs

[4] Surveys Identify Barriers to Participation in Clinical Trials, *JNCI*. 2000; 92: 1556-8.

(i.e., the Consumer Advocates in Research and Related Activities and the Director's Consumer Liaison Group) to identify ways to best involve patient advocacy groups in enhancing patient awareness of clinical trials.

Scientific Steering Committee and Cooperative Group Meetings

Semi-annual meetings with appropriate Scientific Steering Committee and Cooperative Group representatives will create a forum to promote NCI's educational outreach programs and identify ways in which OESI and OC resources can be used to increase community awareness of NCI clinical trials. Regular meetings between clinical trial investigators and the NCI clinical trial education and promotions staff will ensure that educational and promotional messages target the needs of both investigators and patients and will help create best practices for enhancing patient awareness about clinical trials.

Enhancement Initiative 2:

Expand current outreach programs to increase the recruitment of minority populations to cancer clinical trials.

Rationale:

A recent cross-sectional analysis of Cooperative Group clinical trials from 2000 through 2002 found that racial and ethnic minorities were less likely to enroll in Cooperative Group cancer trials than were whites, with the proportion of African American trial participants declining in recent years.[5] Ethnically diverse populations in the United States are growing rapidly, and the incidence of specific cancers is higher in certain ethnic groups. For example, the incidence of colon, rectal, lung and bronchus cancers in Alaska Natives and African American men and women is higher than that of other ethnic groups, and death rates from prostate cancer among African American men are almost twice that of white men. It is vital that these and other minority populations be better represented in trials designed to address those cancers that affect them most severely.

Implementation Plan:

NCI will promote and expand known best practices for recruitment of minority populations by providing additional funds for the following proven initiatives.

Pilot Minority Outreach/Navigator Program

The Clinical Trials Patient Navigator (CTPN) program, established by the Cancer Disparities Research Partnership Program, was designed to help overcome barriers to trial

[5] Murthy, V.H. *et al*., Participation in Clinical Trials, *JAMA.* 2004; 291: 2720-6.

participation among minority populations, and initial reports suggest that these CTPNs are having a positive effect on recruitment and retention. NCI should continue to promote Patient Navigators where they have been successful in recruiting large numbers of minority populations to trials.

Minority-Based Community Clinical Oncology Program (MBCCOP)

NCI launched the Minority-Based Community Clinical Oncology Program (MBCCOP) in 1990 to support practicing oncologists who serve large minority populations and to facilitate the transfer of new technologies in treatment and cancer prevention practices to minority communities and their physicians. Although MBCCOPs comprise less than 20 percent of the CCOP network grantees, they have contributed 33 percent of the CCOP's minority accrual and 7 percent of the minority patients enrolled by all NCI Cooperative Group members and affiliates. The MBCCOPs are well positioned to mentor new investigators as they develop the necessary infrastructure and experience to successfully compete for MBCCOP funding. The NCI should fund more MBCCOPs and initiate a starter program to build the infrastructure necessary to compete for a MBCCOP.

Minority Institution/Cancer Center Partnership Programs

The Minority Institution/Cancer Center Partnership program, sponsored by the Comprehensive Minority Biomedical Branch of the NCI, was established to facilitate research, education, training, and outreach to the minority community and to minority researchers, with the goal of improving the participation of minorities in all aspects of cancer research. This approach brings together Minority-Serving Institutions and Cancer Centers to take advantage of their expertise in educating ethnic minorities and engaging in research, training, and career development activities respectively. One of the basic concepts of the program is to support and generate NIH/NCI peer-reviewed grant applications and funding for minority scientists and programs that focus on cancers that disproportionately affect minority populations. Three mechanisms of support should be made more robust with additional funding: Planning Grants for Minority Institution/Cancer Center Collaborations (P20 grants), Cooperative Planning Grant for Comprehensive Minority Institution/Cancer Center Partnership (U56 grants) and the Comprehensive Minority Institution/Cancer Center Partnership (U54 grants).

Enhancement Initiative 3:

Develop approaches for enhancing adoption of centralized Institutional Review Board processes.

Rationale:

Institutional review requirements for human subjects protection have become inefficient to implement and often delay the opening of trials. This is especially true for large, multisite trials, which can require review by many different Institutional Review Boards

(IRBs). Furthermore, since the median cost for IRB review at academic medical centers was nearly $750,000 per year in 2002[6], the potential for cost savings is substantial.

In 2001, NCI created a Central Institutional Review Board (CIRB) in consultation with the DHHS Office of Human Research Protections (OHRP). Over the succeeding years, as operational efficiencies have been implemented and the benefits of CIRB use have become more widely appreciated, use of the CIRB has grown steadily. However, despite statements from both OHRP and FDA that a properly constituted centralized IRB process can fully meet the requirements of Federal law, and the demonstrated capability of the NCI CIRB process to substantially reduce local administrative burden without delaying startup of patient accrual, there remains resistance to the utilization of the CIRB process for facilitated review, largely among legal and senior research administration staff at major academic institutions.

Implementation Plan:

Barrier Analysis

NCI will conduct a systematic analysis of barriers to acceptance of the CIRB facilitated review process among legal staff, senior research administration staff (including Research Vice-Presidents), and IRB administrators at institutions conducting NCI-funded clinical trials. The goal is to identify the nature of the barriers, (e.g., lack of understanding of OHRP and FDA guidelines, fear of liability, etc.) as well as to identify any remaining shortcomings in the operation of the NCI's CIRB. Based on the findings, NCI will identify steps that can be taken to mitigate the concerns and enhance the rate of adoption of the CIRB process. Because the issues raised by CIRB are not unique to cancer research, NCI will work with NIH leadership, and participate as appropriate in initiatives by independent organizations such as the AAMC, to facilitate broader use of centralized IRB review.

Cost Savings Analysis

NCI will fund an analysis of the potential cost savings that would result from an institution's use of the CIRB facilitated review process and disseminate its findings to the community. Evaluation of the time savings and efficiencies to be gained from utilizing CIRB facilitated review will be an integral part of the cost analysis.

Promote Regional IRB Use

NCI will encourage the use of "regional" IRBs for review of cancer clinical trials. These regional IRBs allow hospitals, community oncologists, or academic medical centers to have a protocol activated at multiple sites based on approval by a single IRB rather than requiring approval from multiple, site-specific IRBs. Such regional IRBs have already

[6] Sugarman, J., et al., The Cost of Institutional Review Boards in Academic Medical Centers, *N Engl J Med*, 2005; 352: 1825-7.

been developed by several CCOPs and by Cancer Centers in single urban areas. These regional IRBs would not replace or compete with the NCI CIRB, but would provide the local IRB oversight function inherent in the CIRB process and facilitate community physician participation in clinical trials.

Enterprise-Wide Initiatives

Introduction:

The initiatives outlined in the preceding sections represent an enormous opportunity to enhance the NCI clinical trials enterprise. They will, however, require substantial coordination, management, and oversight to be successful in improving the quality, efficiency, and effectiveness of NCI clinical trials without introducing unwanted complexities and delays. Therefore it is essential that NCI also enhance its internal organizational structure to effectively address these challenges.

Initiative 1:

Establish a permanent clinical trials subcommittee of the NCAB to advise the NCI Director on the conduct, oversight, and implementation of clinical trials across the Institute.

Rationale:

The CTWG has served as a strong catalyst for change, and was empowered and strengthened by broad representation of external stakeholders in the cancer clinical trials enterprise. To take this effort forward, it is essential that the NCAB establish a similar standing group of external experts to provide oversight for implementation of the initiatives proposed by the CTWG and to guide the enterprise into the future.

Implementation Plan:

A Clinical Trials Oversight Subcommittee of the NCAB will be established to advise the NCI Director on progress made in implementing the CTWG recommendations. The Subcommittee will provide oversight for the Director on a continuing basis on the conduct of clinical trials across the Institute. Membership will include standing members of the NCAB and other NCI Boards, as well as ad hoc members, so that the Subcommittee consists of a broad group of clinical trial experts representing extramural clinical investigators, community oncologists, other oncology health care providers, regulatory agencies, CMS, industry, and patient advocates.

Initiative 2:

Develop a coordinated organizational structure within the NCI to manage the entire clinical trials enterprise supported by the Institute.

Rationale:

Achieving the full benefits of an enhanced system for coordination and prioritization of clinical trials will be difficult if the currently separate and independent management of clinical trials by several NCI Divisions is not more closely integrated. The goal is to develop a structure that leverages the scientific and managerial strengths of the Divisions and coordinates their efforts to build an efficient, interactive, and collaborative process for ensuring that the investment in clinical trials is optimal across the Institute.

Implementation Plan:

The NCI Director will appoint an internal committee composed of the senior leaders of all Divisions who are responsible for clinical trials to develop detailed recommendations for restructuring the internal NCI management of clinical trials to achieve the objectives of the CTWG initiatives and to provide ongoing integration and oversight of clinical trials supported by NCI.

Evaluation and Outcome Measures

Introduction:

No major restructuring of an ongoing enterprise such as the NCI-funded cancer clinical trials program should be undertaken without establishing mechanisms to evaluate the success of the restructuring effort. Evaluation should be an integral part of program management, and should address both process and outcomes. Process assessment is important in order to have confidence that the effort is proceeding appropriately during its initial phase, as well as to create a basis for charting a revised course of action if needed. Outcomes assessment is essential to confirm that the effort is achieving its goals.

Successful evaluation of clinical research programs presents several challenges. First, it is not possible to fully capture all of the important dimensions of performance using purely objective and quantitative measures. The outcome measures must include a judicious blend of qualitative and quantitative, objective and subjective measures. Second, the results of clinical research are necessarily somewhat unpredictable, and can depend to a significant degree on factors beyond the control of the participants. And third, clinical research is a complex system in which multiple internal and external factors interact in many different ways – some of which are observable, and some not – to affect outcomes. Thus, attribution of observed outcomes to particular program policies, organizational structures, or management decisions can be difficult.

An evidence-based approach is essential. The determination of success or failure and decisions on any needed course corrections will not be automatic or mechanical, but a matter of judgment by experts in the field. However, this expert evaluation must be informed by systematic, structured empirical data so that there will be a shared basis for discussion and decision-making. The measures used do not serve as the sum total of the evaluation, but as essential "raw material" for a larger process of expert judgment in which the broad oncology research community must participate.

The needed measures fall into three categories:

- Program management process measures that evaluate implementation of the cancer clinical trials restructuring effort.
- System performance process measures that evaluate the effect of changes in operational processes on the design, prioritization, and conduct of cancer clinical trials.
- System outcome measures that assess the results which ultimately matter – an increased number of useful therapies for patients and improved targeting of therapies to the specific patients who will benefit.

To evaluate the impact of the proposed restructuring, it is essential to conduct a baseline evaluation of the selected measures prior to implementation. Only then can the effect of change be recognized. It is also essential to set realistic timelines for achievement of the objectives so that evaluation is not attempted either too early or too late in the process.

For example, certain process measures may come into play only after other processes on which they depend have been completed. Similarly, it may be a matter of years before it is reasonable to expect certain outcomes to be apparent. Nevertheless, many process measures can be fruitfully assessed at intervals to document the progress of the restructuring initiatives.

The measures proposed below are not fully operationalized, and thus should be viewed as suggested topic areas rather than actual measures. In addition, as well defined measures do not currently exist for many of the elements of the NCI-supported cancer clinical trials program, establishing the specific measures will be an ongoing and iterative process.

NCI will engage experienced evaluation specialists to assist in development of the definitions, survey instruments, statistical adjustments, and other tools required for the evaluation measures to be practical and valid and to conduct the evaluations. These specialists will also determine the appropriate timing for examining the various measures in the context of implementation timelines and the nature of the impacts envisioned. The specialists will conduct a baseline evaluation of the current system as soon as possible to provide a reliable basis for ascertaining the value of the restructuring effort. The results of this baseline evaluation will be analyzed to determine whether the chosen measures are valid or should be eliminated or revised.

Program Management Process Measures:

These measures will be tracked by NCI on a continuing basis, as part of its management of the restructuring process, and will be assessed in light of the proposed implementation plan and timeline. Questions to be addressed include the following:

- Were the tasks initiated on time?
- Did they follow the implementation plan as outlined?
- If obstacles were encountered, were alternate plans implemented quickly and effectively?
- Were the tasks accomplished on time or were timelines revised in a timely and realistic fashion?

System Performance Process Measures:

The restructuring effort has three key process objectives:

- Improved communication and coordination, leading to more collaboration and cooperation in the design and conduct of cancer clinical trials.
- Enhanced scientific quality of cancer clinical trials through a more strategically focused and transparent prioritization process involving the broad oncology community.
- Enhanced operational efficiency to achieve more timely and cost-effective initiation and conduct of cancer clinical trials.

To accomplish these objectives, the restructuring effort envisions implementing new structures, processes, and behaviors on the part of participants in the system. The system performance measures must therefore provide empirical evidence of whether the new structures and processes are being used effectively, whether the targeted behaviors are changing in the intended ways, and whether the impacted components and the system as a whole are in fact becoming more efficient, more collaborative, more transparent, and of higher scientific quality. Supplemental measures should also be used to assure that the new objectives are not achieved at the expense of other valued characteristics of the current cancer clinical trials system.

Some of the system performance characteristics can be assessed via objective measures, while others must be assessed subjectively, through a systematic and transparent process of soliciting expert opinion. It is important to remember that no single measure will provide a conclusive indicator of success, nor a basis for attribution of cause and effect. Rather each measure must be combined with the others and included in a larger comprehensive evaluation by a broad range of critical stakeholders.

Described below are some examples of the types of measures that might be developed by the evaluation experts retained to develop the evaluation process. These should not be considered either definitive or comprehensive, but rather illustrative of the logic to be applied.

Coordination New Initiative 2

Realign NCI funding, academic recognition, and other incentives to promote collaborative team science and clinical trial cooperation.

1. Number of clinical trials that involve collaboration across mechanisms and resources (e.g., interactions among SPOREs, Cooperative Groups, Cancer Centers, etc.). Evaluation at 0, 2 and 5 years.
2. Perception by academic clinical investigators of the degree to which NCI funding and recognition policies reward participation in collaborative clinical trials. Evaluation at 0, 2 and 5 years.
3. Ongoing clinical research activities by investigators funded through new Clinical Investigator awards. Evaluation at 5 and 7 years.
4. Credit awarded for participation in NCI sponsored collaborative clinical trials in promotion/tenure committee guidelines. Evaluation at 0, 5 and 7 years.
5. Perception by academic clinical investigators of the value accorded at their institutions to participation in collaborative clinical trials. Evaluation at 0, 5 and 7 years.

Prioritization/Scientific Quality New Initiative 2

Establish a network of Scientific Steering Committees to address design and prioritization of phase III efficacy trials that leverages current Intergroup, Cooperative Group, SPORE, and Cancer Center structures and involves the broad oncology community.

1. Time from initiation of Phase III concept discussions to launch of trial accrual. Evaluation at 0, 2 and 5 years.
2. Extent of duplication in NCI's portfolio of phase III clinical trials. Evaluation at 0, 2 and 5 years.
3. Perception by extramural clinical investigators of the transparency, fairness, quality and efficiency of the phase III trial prioritization process. Evaluation at 0, 2 and 5 years.
4. Perception by community oncologists and patient advocates of the extent to which phase III protocols incorporate their input and have designs and clinical outcomes attractive to patients and treating physicians. Evaluation at 0, 2 and 5 years.
5. Quality of phase III concepts submitted to CTEP including importance of clinical question addressed, degree of innovation, lack of duplication, strength of proposed correlative science, etc. Evaluation at 0, 2 and 5 years.

Standardization New Initiative 1

Promote establishment of national clinical trial information technology infrastructures that are fully interoperable with NCI's cancer Bioinformatics Grid.

1. Number of clinical trial management modules implemented in caBIG. Evaluation at 1 and 3 years.
2. The extent to which the caBIG standards and tools have been implemented in the cancer clinical trials community. Evaluation at 2 and 5 years.
3. The number of caBIG compliant systems developed by vendors to service the cancer clinical trials community. Evaluation at 2 and 5 years.
4. Level of caBIG interoperability of IT systems for clinical trial management throughout the broad oncology community. Evaluation at 2 and 5 years.
5. Perception of clinical investigators of the utility of caBIG in mounting and managing a clinical trial. Evaluation at 2 and 5 years.
6. Cost and time savings achieved through IT interoperability. Evaluation at 5 and 7 years.

Operational Efficiency New Initiative 1

Restructure the funding model for Phase III efficacy trials to incentivize more rapid rates of patient accrual.

1. Efficiencies in clinical trial management and administration identified and implemented. Evaluation at 2 and 4 years.
2. Distribution of patient accrual at high and medium accruing sites and number of sites below economically viable accrual levels. Evaluation at 0, 3 and 6 years.
3. Cost savings achieved due to shift of patient accrual to highly accruing, more efficient sites. Evaluation at 3 and 6 years.
4. Perception of clinical investigators concerning the degree to which NCI funding is structured to incentivize patient accrual. Evaluation at 0, 3 and 6 years.

System Outcome Measures:

The most important and meaningful outcome measures for the restructuring effort are the degree to which the changes achieve the goal of enhanced clinical trial success and an enhanced number of new treatments reaching patients more quickly. The most important measures are the following:

- Rate of accrual, time to completion, and cost effectiveness for NCI-supported phase III protocols.
- Number of NCI-supported trials that provide results critical for guiding new therapeutics and diagnostics development.
- Number of new biomarkers validated in NCI-supported trials that enable better targeting of cancer therapies.
- Number of revisions of major treatment guidelines (e.g., ASCO, etc.) to reflect new knowledge gained from NCI-supported trials.

Timeline and Budget

Timeline:

Implementation of the 22 initiatives recommended by the CTWG will require at least four to five years to complete, although the majority are projected to be implemented by the end of year three. Moving from initial implementation to routine practice will then require another two to three years. A schedule of key activities and milestones associated with each initiative is presented in Table 1 (see Appendix B). Major items for each year include the following:

Year 1:

Coordination Initiatives

- Initiate development of comprehensive clinical trials database.
- Expand the CTSU to cover SPORE and Cancer Center trials.
- Develop policies and procedures governing joint NCI/FDA meetings concerning new agents; begin to conduct joint meetings.

Prioritization/Scientific Quality Initiatives

- Establish Investigational Drug Steering Committee for design and prioritization of early phase drug development trials.
- Establish initial Scientific Steering Committees for the design and prioritization of phase III trials.
- Convene initial State-of-the-Science Meetings.
- Convene initial community oncologist and patient advocate focus groups.
- Define criteria for prioritization of correlative science and quality of life proposals.

Standardization Initiatives

- Increase clinical investigator representation on the caBIG Clinical Trials Management System workspace.
- Develop strategies to achieve clinical trial IT interoperability.
- Initiate process of achieving industry/FDA concurrence on standard Case Report Forms incorporating Common Data Elements.
- Initiate development of a credentialing system for investigators and sites.

Operational Efficiency Initiatives

- Conduct analysis of phase III clinical trial costs.
- Initiate analysis of institutional barriers to timely trial initiation at sites.
- Initiate regular interactions of NCI education and communications staff with patient advocacy groups and clinical investigators to increase patient and public awareness and understanding of clinical trials.
- Implement additional funding for minority outreach programs.
- Initiate analysis of institutional barriers to adoption of the NCI CIRB facilitated review process.

Enterprise-Wide Initiatives

- Establish NCAB Clinical Trials Oversight Subcommittee.
- Restructure NCI clinical trials management.
- Develop an evaluation system and implement baseline assessment.

Year 2:

Coordination Initiatives

- Expand NCI clinical trials database review capacity.
- Adjust grant data reporting requirements.
- Modify NCI award guidelines to reward collaboration.
- Institute new forms of NCI recognition to reward collaboration.
- Initiate interactions with medical school deans on academic incentives.
- Initiate awareness campaign for NCI/FDA expedited review process.
- Establish NCI/CMS process to select studies appropriate for reimbursement.

Prioritization/Scientific Quality Initiatives

- Establish additional Scientific Steering Committees.
- Convene additional State-of-the-Science Meetings.
- Convene additional community oncologist and patient advocate focus groups.
- Establish community oncologist and patient advocate Steering Committees.
- Establish budget for correlative science/quality of life studies and initiate funding.
- Create initial standards documents for measurement, analysis and reporting of biomarker data in association with clinical trials.

Standardization Initiatives

- Create web-based trial initiation tool in caBIG.
- Complete development of standard Case Report Forms with industry/FDA concurrence.
- Hold conference on standard clinical trial contract clauses with NCI, industry and clinical trial sites.

Operational Efficiency Initiatives

- Restructure phase III trial funding model.
- Begin to increase funding for high accruing sites.
- Complete analysis of institutional barriers to timely trial initiation at sites.
- Develop approaches to enhance adoption of NCI CIRB facilitated review process.

Enterprise-Wide Initiatives

- Evaluate progress of specific initiatives based on implementation plan timeline.

Year 3:

Coordination Initiatives

- Fully implement the clinical trials database with all data being routinely submitted.

Prioritization/Scientific Quality Initiatives

- Evaluate phase III prioritization system.
- If successful, initiate expanded phase III prioritization system implementation.
- Evaluate feasibility of integrating prioritization of phase II trials.

Standardization Initiatives

- Complete internal NCI IT system harmonization with caBIG.
- Implement standard Case Report Forms.
- Develop system to credential investigators and sites.
- Reach agreement on standard clinical trial contract clauses with stakeholders.

Operational Efficiency Initiatives

- Implement solutions for reducing institutional barriers to timely trial initiation at sites.
- Implement approaches for enhancing adoption of NCI CIRB facilitated review process.

Enterprise-Wide Initiatives

- Evaluate progress of specific initiatives based on implementation plan timeline.

Years 4-5:

Coordination Initiatives

- Implementation complete.

Prioritization/Scientific Quality Initiatives

- Complete implementation of prioritization system for all phase III trials.
- If judged feasible, initiate integrated prioritization of phase II trials.

Standardization Initiatives

- Achieve overall IT interoperability across NCI-funded cancer clinical trials system.
- Create registry of credentialed investigators and sites.

Operational Efficiency Initiatives

- Implementation complete.

Enterprise-Wide Initiatives

- Evaluate progress of specific initiatives based on implementation plan timeline.

Budget:

The estimated cost for implementing the CTWG initiatives is presented in Tables 2 and 3 (see Appendix B). Table 2 presents the costs by category – Extramural, Analysis/Development Projects, NCI Operational Activities, and Meeting Support. Table 3 presents the costs by year. The incremental cost for Year 1 (FY 06) is $7.1M, increasing to $20.6M in Year 2 (FY07), and then reaching a steady state of approximately $29M annually by Year 3.

By far the largest portion of this incremental expense ($21.5M or 75%) is provided to the extramural community to enhance the quality and efficiency of clinical trials. Of the remaining 25%, $2.8M (10%) directly supports the clinical trial database that provides clinical investigators, practicing oncologists, patients, and NCI staff with comprehensive, up-to-date information about all NCI-supported clinical trials. Another 10% ($2.9M) supports the enterprise-wide prioritization system, involving all the critical stakeholders, for ensuring that NCI supports the best-designed trials, addressing the most important questions and leveraging the most significant scientific advances. The final 5% ($1.5M) supports the management structure within NCI necessary to ensure that the initiatives are implemented and maintained in a manner that truly transforms the national cancer clinical trials enterprise.

APPENDICES

Appendix A

CTWG Meeting Dates and Acknowledgments

Appendix B

Table 1: Implementation Timeline

Table 2: Estimated Implementation Budget by Category

Table 3: Estimated Implementation Budget by Year

Appendix A
Meeting Dates and Acknowledgments

CTWG Meeting Dates

2004

January 29 & 30
Initial Conference Calls

February 26 & 27
CTWG Conference Calls

April 22 & 23
CTWG Conference Calls

May 24
First Face-to-Face Meeting of the CTWG
Chicago, Illinois

August 27
Face-to-Face Meeting of the CTWG
Chicago, Illinois

September 23 & 24
CTWG Conference Calls

October 14 & 15
CTWG Conference Calls

November 17
Face-to-face meeting of the CTWG
Chicago, Illinois

December 9 & 10
CTWG Conference Calls

2005

January 21 & 27
CTWG Conference Calls

February 9 & 10
Face-to-face meeting of the CTWG
Chicago, Illinois

February 17
Subcommittee Chairs Report to the NCAB
Bethesda, Maryland

March 3 & 4
CTWG Conference Calls

March 17 & 18
CTWG Conference Calls

March 31 & April 1
Face-to-Face Meeting of the CTWG
Chicago, Illinois

April 28 & 29
Face-to-Face Meeting of the CTWG
Chicago, Illinois

May 3
Face-to-Face Meeting of the CTWG
Bethesda, Maryland

May 19 & 20
CTWG Conference Calls

June 7
Final Report to the NCAB
Bethesda, Maryland

Acknowledgments

In addition to all of the dedicated members of the Clinical Trials Working Group, there have been several other individuals who played very important roles facilitating the efforts of the CTWG, from its inception through the development of this report:

Margaret Holmes, Ph.D., Director of NCI's Office of Grant Program Coordination, and **Clarissa L. Douglas**, Program Coordinator in the Office of Grant Program Coordination, worked tirelessly to support the formation of the CTWG, its initial conference calls and face-to-face meetings, the evaluation of current issues facing NCI's clinical trials structure, the elaboration of the CTWG's working structure, and the initiation of the CTWG web site.

Tom Benthin was very helpful in facilitating the initial face-to-face meetings of the group and in providing graphic representations of these activities.

Clint Malone from the NCI Center for Bioinformatics was exceptionally helpful in developing both the CTWG website and the web forums that were essential to the collection of input for the CTWG's initial recommendations to the NCAB from the extramural community.

Dr. David Dilts, Professor of Management at the Vanderbilt University School of Business, was kind enough to share his detailed analysis of the "bottlenecks" in the cancer clinical trials process at the Vanderbilt-Ingram Comprehensive Cancer Center with the entire CTWG, as well as his preliminary recommendations regarding how the elimination of such barriers might be approached.

Drs. Stephen Grubbs and Shaker Dakhil, from the Delaware and Wichita CCOPs, respectively, provided critical insights into the essential role of community oncologists in the NCI-funded cancer clinical trials system; these insights had a major impact on the development of this report.

Kristin Hinkle was exceptionally effective managing conference calls and the scheduling of face-to-face meetings for the CTWG.

Maureen Johnson, Ph.D., Special Assistant, Office of the NCI Director, coordinated all of the activities of the CTWG as its Executive Director over the past nine months. There is no question that her extraordinary commitment to the CTWG played a fundamental role in the creation of the initiatives outlined in this report.

Science and Technology Policy Institute (STPI) of the Institute for Defense Analyses: The critical roles of **Judith Hautala, Ph.D.** (Lead Coordinator), and **Oren Grad, M.D., Ph.D., Yumi Ando, M.D., M.P.H.,** and **Todd Falcone** in the elaboration of this document would be difficult to overestimate. Each member of the STPI team was essential in moving the deliberations of the CTWG, from the development of preliminary recommendations to the ultimate completion of a document that outlines a series of initiatives with plans for their implementation.

Appendix B

Table 1: Implementation Timeline

Initiative	Key Milestones and Activities			
Coordination	**Year 1 (Oct. 2005-Sept. 2006)**	**Year 2 (Oct. 2006-Sept. 2007)**	**Year 3 (Oct. 2007- Sept. 2008)**	**Years 4 – 5 (Oct. 2008-Sept. 2010)**
Comprehensive clinical trials database	Establish implementation task force Begin to develop database Define data to deposit Determine data submission procedures Determine access controls Investigate grant data reporting requirements	Continue to develop database Create report templates Expand NCI database review capacity Adjust grant data reporting requirements	Run pilot test with extramural users Database fully implemented by March Routine submission of all trial data in place by September	
Align incentives to reward collaboration	Begin to modify NCI award guidelines Begin to create new forms of NCI recognition Develop strategies for medical school deans Expand CTSU to cover SPORE and Cancer Center trials	Modify NCI award guidelines Institute new forms of NCI recognition Begin interactions with medical school deans/AAMC/IOM	Continue to interact with medical school deans/AAMC/ IOM	Continue to interact with medical school deans/AAMC/ IOM
Joint FDA/NCI meetings	Develop policies and procedures for meetings Develop non-disclosure agreements Begin joint meetings by July.			

Enhance industry awareness of NCI/FDA expedited review process	Develop communication plan	Initiate awareness campaign	Evaluate the campaign's effectiveness	
Collaborate with CMS on study funding	Begin to establish process to select studies	Establish process to select studies		

Table 1, Continued: Implementation Timeline

Initiative	Key Milestones and Activities			
Prioritization	**Year 1 (Oct. 2005-Sept. 2006)**	**Year 2 (Oct. 2006-Sept. 2007)**	**Year 3 (Oct. 2007- Sept. 2008)**	**Years 4 - 5 (Oct. 2008-Sept. 2010)**
Investigational drug trial prioritization	• Establish Investigational Drug Steering Committee • Organize first strategic meeting • Begin routine prioritization activities by June			
Phase III trial prioritization	• Establish initial Scientific Steering Committees • Convene initial State-of-the-Science meetings • Convene initial community oncologist/patient advocate focus groups	• Establish additional Scientific Steering Committees • Convene additional State-of-the-Science meetings • Convene additional focus groups	• Evaluate prioritization system • Begin expanded prioritization system implementation if successful	• Complete implementation of expanded prioritization system
Community Oncologist/Patient Advocate Steering Committees		• Establish Steering Committees		
Phase II trial integration	• Begin presentations at State-of-the-Science meetings	• Begin data submission to database	• Routine database submission by September • Evaluate feasibility of	• Begin integrated prioritization if feasible

			integrating prioritization	
Correlative science / quality of life funding	• Define criteria for study prioritization • Establish budget	• Criteria for prioritization established by October • Budget established by October • Initiate funding		
Correlative science standards	• Define technology categories	• Create initial standards documents • NCI implements standardization requirements for proposals	• Begin ongoing review and update	

Table 1, Continued: Implementation Timeline

Initiative	Key Milestones and Activities			
Standardization	**Year 1 (Oct. 2005-Sept. 2006)**	**Year 2 (Oct. 2006-Sept. 2007)**	**Year 3 (Oct. 2007- Sept. 2008)**	**Years 4 – 5 (Oct. 2008-Sept. 2010)**
caBIG interoperability	• Increase clinical investigator representation on Clinical Trials Management Systems workspace • Develop strategy to harmonize internal NCI IT systems • Develop strategy to achieve overall IT interoperability of NCI funded clinical trial system	• Create web-based trial initiation tool	• Complete internal NCI IT system harmonization	Overall IT interoperability of NCI-funded clinical trials system achieved by September 2010
FDA/industry concurrence on standard CRF library	• Begin to harmonize/expand NCI standard CRFs with industry and FDA involvement	• Complete development of standard CRFs with industry/FDA concurrence	• Implementation of standard CRFs by September • Begin annual review and update	
Credentialing system	• Create Task Force • Develop credentialing criteria	• Credentialing criteria developed by June • Begin to develop system to credential investigators and sites	• Develop system to credential investigators and sites	• Complete system to credential investigators and sites by January, 2009 • Create registry

Standard clinical trial contract clauses		• Conduct stakeholder conference • Develop standard contract clauses	• Reach agreement on contract clauses with stakeholders	• Promote use of contract clauses by industry and clinical trial sites

Table 1, Continued: Implementation Timeline

Initiative	Key Milestones and Activities			
Operational Efficiency	**Year 1 (Oct. 2005-Sept. 2006)**	**Year 2 (Oct. 2006-Sept. 2007)**	**Year 3 (Oct. 2007- Sept. 2008)**	**Years 4 – 5 (Oct. 2008-Sept. 2010)**
Restructure phase III clinical trials funding model	• Analyze phase III clinical trial costs	• Analysis completed by March • Restructure funding model based on analysis • Begin to increase funding for high accruing sites		
Identify institutional barriers that delay trial initiation	• Initiate analysis	• Analysis completed by September	• Develop solutions for reducing barriers • Begin to implement solutions	• Continue to implement solutions
Increase patient/public awareness of clinical trials	• Establish interactions between OC and OESI and clinical investigators • Establish interactions between OC and OESI and patient advocacy groups			
Increase minority outreach	• Implement additional funding for minority outreach programs			
Reduce IRB administrative burden	• Initiate analysis of barriers to CIRB adoption	• Analysis completed by March • Develop approaches to enhance CIRB adoption	• Implement approaches to enhance CIRB adoption	

Table 1, Continued: Implementation Timeline

Initiative	Key Milestones and Activities			
Enterprise-Wide	**Year 1 (Oct. 2005-Sept. 2006)**	**Year 2 (Oct. 2006-Sept. 2007)**	**Year 3 (Oct. 2007- Sept. 2008)**	**Years 4 - 5 (Oct. 2008-Sept. 2010)**
NCAB Clinical Trials Oversight Subcommittee	• Establish oversight subcommittee			
Restructure NCI clinical trials management	• Restructure NCI management			
Evaluation and outcome measures	• Develop evaluation system • Take baseline measurements of programs to be evaluated	• Evaluate progress of specific initiatives based on implementation plan timeline	• Evaluate progress of specific initiatives based on implementation plan timeline	• Evaluate progress of specific initiatives based on implementation plan timeline

Table 2: Estimated Implementation Budget by Category

Initiative	Expenses				
Coordination	**Extramural**	**Analysis/Development Projects**	**NCI Operational Activities**	**Meeting Support**	**Total**
Create comprehensive clinical trials database	Data Reporting Costs[7] Yr 1 $0.0M Yr 2 $0.0M Yr 3 $2.0M Yr 4 $1.0M Yr 5 $0.0M	Database Develpmt/Maint Yr 1 $1.0M Yr 2 $1.5M Yr 3 $0.5M Yr 4 $1.8M Yr 5 $1.8M	NCI Data Review Staff Yr 3-5 $250K/yr Data Review Contract Yr 3-5 $750/yr	Implementation Task Force Yr 1 $250K Yr 2 $250K Yr 3 $250K	Yr 1 $1.3M Yr 2 $1.8M Yr 3 $3.8M Yr 4 $3.8M Yr 5 $2.8M
Align incentives to reward collaboration	Clinical Inv. Award Yr 2-5 $1.0M/yr SPORE/Cancer Center CTSU Trials $0.5M/yr Yr 2 $0.75M/yr Yr 1	N/A	See Note 1	N/A	Yr 1 $0.5M Yr 2 $1.8M Yr 3 $2.0M Yr 4 $2.0M Yr 5 $2.0M
Develop joint FDA/NCI meetings	Yr 3-5 $1.0M/yr N/A	N/A	See Note 1	N/A	See Note 1
Enhance industry awareness of NCI/FDA expedited	N/A	N/A	See Note 1	N/A	See Note 1

[7] Costs not covered by grants; no data reporting in Yr1-2; grants modified at renewal; therefore the costs are partially covered by grants in Yr 3-4 and completely in Yr 5.

review process					
Collaborate with CMS on study funding	N/A	N/A	See Note 1	N/A	See Note 1

Note 1: Included in NCI clinical trials management expenses (see page 74).

Table 2, Continued: Estimated Implementation Budget by Category

Initiative	Expenses				
Prioritization	**Extramural**	**Analysis/Development Projects**	**NCI Operational Activities**	**Meeting Support**	**Total**
Investigational drug trial prioritization	N/A	N/A	Clin Trials Mgmt Staff Yr 1-5 $100K/yr Other NCI Staff Yr 1-5 $250K/yr	Investigational Drug Steering Committee[8] Yr 1-5 $150K/yr	Yr 1 $500K Yr 2 $500K Yr 3 $500K Yr 4 $500K Yr 5 $500K
Phase III trial prioritization	N/A	N/A	Clin Trls Mgmt & Other NCI Staff Yr 1 $200K + $150K Yr 2 $200K + $300K Yr 3-5 $400K + $450K	SOS[9] & Steering Com[10] Yr1 2SOS/10SC $400K Yr2 4SOS/20SC $800K Yr3 6SOS/30SC $1.1M Yr4 8SOS/40SC $1.3M Yr5 10SOS/50SC $1.5M	Yr 1 $0.75M Yr 2 $1.3M Yr 3 $2.0M Yr 4 $2.2M Yr 5 $2.4M
Establish Community Oncologist/Patient Advocate Steering	N/A	N/A	N/A	See Note 2	See Note 2

[8] Four meetings per year; 30 members
[9] State of Science Meeting; 50 attendees $80K/meeting
[10] Scientific Steering Committee Meetings; size of Committee and number of meetings per year varies with disease

Committees					
Phase II trial prioritization integration	N/A	N/A	See Note 2	N/A	See Note 2
Correlative science / quality of life funding	Yr 2 $ 5M Yr 3-5 $10M/yr	N/A	See Note 1	N/A	Yr 1 $ 0 Yr 2 $ 5M Yr 3 $10M Yr 4 $10M Yr 5 $10M
Correlative science standards	N/A	N/A	See Note 1	See Note 1	See Note 1

Note 1: Included in NCI clinical trials management expenses (see page 74).
Note 2: Included in phase III trial prioritization expenses (this page).

Table 2, Continued: Estimated Implementation Budget by Category

Initiative	Expenses				
Standardization	**Extramural**	**Analysis/Development Projects**	**NCI Operational Activities**	**Meeting Support**	**Total**
Promote caBIG interoperability	N/A	Interoperability Analyses Yr 1 $500K (NCI intrnl) Yr 2 $500K (extramural) Trial Initiation Tool Yr 2 $500K	N/A	Additional Clinical Trials Workspace Expense Yr 1-5 $250/yr	Yr 1 $750K Yr 2 $1.3M Yr 3 $250K Yr 4 $250K Yr 5 $250K
FDA/Industry concurrence on standard CRF library	N/A	N/A	See Note 1	See Note 1	See Note 1
Credentialing system[11]	N/A	N/A	See Note 1	See Note 1	See Note 1
Standard clinical trial contract clauses	N/A	N/A	See Note 1	See Note 1	See Note 1

Note 1: Included in NCI clinical trials management expenses (see page 74).

[11] Assume cost of establishing credentialing system is paid by professional societies/trade associations.

Table 2, Continued: Estimated Implementation Budget by Category

Initiative	Expenses				
Operational Efficiency	**Extramural**	**Analysis/Development Projects**	**NCI Operational Activities**	**Meeting Support**	**Total**
Restructure phase III clinical trials funding model	High Accrual Supplemnts Yr 1 $0.0M Yr 2 $5.0M Yr 3 $6.0M Yr 4 $7.0M Yr 5 $7.5M	Financial Analysis Yr 1- 2 $500K/yr	See Note 1	N/A	Yr 1 $0.5M Yr 2 $5.5M Yr 3 $6.0M Yr 4 $7.0M Yr 5 $7.5M
Identify institutional barriers that delay trial initiation	N/A	Barrier Analysis Yr 1-2 $350K/yr	See Note 1	N/A	Yr 1 $350K Yr 2 $350K Yr 3 $0 Yr 4 $0 Yr 5 $0
Increase patient/public awareness of clinical trials	N/A	N/A	See Note 1	N/A	See Note 1
Increase minority outreach	Expanded Minority Programs Yr 1 $0.5M Yr 2-5 $2M/yr	N/A	N/A	N/A	Yr 1 $0.5M Yr 2 $2.0M Yr 3 $2.0M Yr 4 $2.0M Yr 5 $2.0M

Reduce IRB administrative burden	N/A	Barrier Analysis Yr 1-2 $100K/yr Cost Savings Analysis Yr 1 $100K	See Note 1	N/A	Yr 1 $200K Yr 2 $100K Yr 3 $0 Yr 4 $0 Yr 5 $0

Note 1: Included in NCI clinical trials management expenses (see page 74).

Table 2, Continued: Estimated Implementation Budget by Category

Initiative	Expenses				
Enterprise-Wide	**Extramural**	**Analysis/Development Projects**	**NCI Operational Activities**	**Meeting Support**	**Total**
NCAB Clinical Trials Oversight Subcommittee	N/A	N/A	N/A	See Note 1	See Note 1
Restructure NCI clinical trials management	N/A	N/A	Clinical Trials Mgmt[12] Yr 1-5 $550K/yr	CTWG Implementation[13] Yr 1 $450K Yr 2 $400K Yr 3 $350K Yr 4-5 $200K/yr	Yr 1 $1.0M Yr 2 $950K Yr 3 $900K Yr 4 $750K Yr 5 $750K
Evaluation and outcome measures	N/A	Evaluation System Developmnt/Measurement Yr 1 $750K Yr 2 $0 Yr 3 $500K Yr 4 $0 Yr 5 $500K	See Note 1	N/A	Yr 1 $750K Yr 2 $0 Yr 3 $500K Yr 4 $0 Yr 5 $500K

Note 1: Included in NCI clinical trials management expenses (this page).

[12] Four professionals including clerical, office expenses, travel, etc.; an additional professional will be added in Yr 3 if the phase III prioritization system is expanded to all diseases. The expenses for managing the prioritization Steering Committees are not included in the total shown; these expenses are included in the investigational drug trial prioritization and phase III trial prioritization expenses (See page 71).

[13] NCAB Subcommittee, Patient Advocate/Community Oncologist Steering Committees and meetings to develop correlative science standards, standard CRFs, credentialing system and standard contract clauses.

Table 3: Estimated Implementation Budget by Year

Initiative	Expenses				
Coordination	**Year 1 – FY06**	**Year 2 – FY07**	**Year 3 – FY08**	**Year 4 – FY09**	**Year 5 – FY10**
Create comprehensive clinical trials database	$1.3M	$1.8M	$3.8M	$3.8M	$2.8M
Align incentives to reward collaboration	$0.5M	$1.8M	$2.0M	$2.0M	$2.0M
Develop joint FDA/NCI meetings	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
Enhance industry awareness of NCI/FDA expedited review process	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
Collaborate with CMS on study funding	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
Prioritization					
Investigational drug trial prioritization	$500K	$500K	$500K	$500K	$500K

Phase III trial prioritization	$750K	$1.3M	$2.0M	$2.2M	$2.4M
Establish Community Oncologist/Patient Advocate Steering Committees	See Note 2	See Note 2	See Note 2	See Note 2	See Note 2
Phase II trial integration	See Note 2	See Note 2	See Note 2	See Note 2	See Note 2
Correlative science / quality of life funding	N/A	$5M	$10M	$10M	$10M
Correlative science standards	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1

Note 1: Included in NCI clinical trials management expenses (see page 77).
Note 2: Included in phase III trial prioritization expenses (this page).

Table 3, Continued: Estimated Implementation Budget by Year

Initiative	Expenses				
Standardization	**Year 1 – FY06**	**Year 2 – FY07**	**Year 3 – FY08**	**Year 4 – FY09**	**Year 5 – FY10**
caBIG interoperability	$750K	$1.3M	$250K	$250K	$250K
FDA/Industry concurrence on standard CRF library	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
Credentialing system[14]	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
Standard clinical trial contract clauses	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
Operational Efficiency					
Restructure phase III clinical trials funding model	$500K	$5.5M	$6.0M	$7.0M	$7.5M
Identify institutional barriers that delay trial initiation	$350K	$350K	N/A	N/A	N/A

[14] Assume cost of establishing credentialing system is paid by professional societies/trade associations.

Increase patient/public awareness of clinical trials	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
Increase minority outreach	$0.5M	$2.0M	$2.0M	$2.0M	$2.0M
Reduce IRB administrative burden	$200K	$100K	N/A	N/A	N/A

Note 1: Included in NCI clinical trials management expenses (see page 77).

Table 3, Continued: Estimated Implementation Budget by Year

Initiative	Expenses				
Enterprise-Wide					
NCAB Clinical Trials Oversight Subcommittee	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
Restructure NCI clinical trials management	$1.0M	$950K	$900K	$750K	$750K
Evaluation and outcome measures	$750K	$0	$500K	$0	$500K
TOTAL	**$7.1M**	**$20.6M**	**$28.0M**	**$28.5M**	**$28.7M**
5 year Total					**$112.9M**

Note 1: Included in NCI clinical trials management expenses (this page).