

Enhancing Cancer Treatment through Improved Understanding of the Critical Components, Economics and Barriers of Cancer Clinical Trials:

A policy focused guidance document
commissioned by C-Change and
the Coalition of Cancer Cooperative Groups

Preface

In June 2005, The Lewin Group, partnered with Lovett Collins Associates, was commissioned by C-Change to conduct a study to determine the cost and time expenditures of cancer clinical trials. The Lewin Group published these findings and elements of success for cancer clinical trials in a document titled, “A Guidance Document for Implementing Effective Cancer Clinical Trials, Version 1.2”.

The following year, The Lewin Group, partnered with Lovett Collins Associates, was commissioned by C-Change and the Coalition of Cancer Cooperative Groups to produce two targeted follow-up documents: a policy document that summarizes the current economic environment of cancer clinical trials for policy makers; and, a web-based resource and guidance document on how to conduct clinical trials for use by clinical trial personnel.

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Executive Summary

This guidance document, “Enhancing Cancer Treatment through Improved Understanding of the Critical Components, Economics and Barriers of Cancer Clinical Trials” was commissioned by C-Change, a national multi-sector cancer collaborative and the Coalition of Cancer Cooperative Groups (CCCG), a non-profit service organization dedicated to improving access to cancer clinical trials. The primary purpose of this document is to improve policy makers’ and other stakeholders’ understanding of the process, economics and barriers related to cancer clinical trials. These barriers will continue to hinder this nation’s ability to introduce new and effective cancer therapies and improve cancer prevention. This document also highlights the necessity of adequate and sustainable public funding to ensure increased participation and effective clinical trial processes.

As stewards of the public system, policy makers will likely need to find ways to positively impact physicians’ and institutions’ abilities to provide clinical trial options to patients by:

- Ensuring adequate public funding for clinical trials;
- Supporting high quality tissue and serum banking systems required to enable pharmacogenomic and genetic research projects to permit more tailored approaches to patient care;
- Ensuring that the regulatory process is more efficient and effective for investigators so more participate in cancer clinical trials and encourage their patients to do so; and
- Promoting general public and physician education about clinical trials in order to ensure adequate participation. In accordance with the National Institutes of Health Revitalization Act of 1993 [Public Law 103-43], the latter includes the adequate representation of women and minority populations in publicly funded clinical research.

By increasing clinical trial participation by investigators and patients through the removal of financial and regulatory barriers, as well as improving the infrastructure to support cancer research through clinical trials, policy makers have the ability to ensure significant and much needed advancements in cancer prevention and treatment.

Current Clinical Trial Environment

The advancement of cancer therapeutics depends largely upon an effective clinical trial process that has sufficient funding to increase visibility and participation by patients and investigators.

One of the most challenging issues to clinical trial efforts is the limited numbers of patients who actually participate. The National Cancer Institute (NCI) frames the issue stating, “we will never know the true effectiveness of a cancer treatment or a way to prevent cancer unless more people are involved in clinical trials.” Only about three percent of US adults with cancer participate in clinical trials – already “far fewer than the number needed to answer the most pressing cancer questions quickly.”¹ The goal of increased clinical trial participation is to increase stewardship of relatively scarce clinical trial resources resulting in a more productive process of inquiry that results, ultimately, in a fundamental societal benefit associated with the development of more readily available and effective cancer therapies.

Advances in cancer biology have significantly changed approaches to cancer treatment. Targeted drug therapies, improved diagnostics and earlier intervention have improved physicians’ ability to care for cancer patients and those at risk, yet have increased the demands for the investigation of new agents and treatment processes. Given the greater demand for such trials, the development and approval process for new therapies has become more protracted.

Furthermore, there is a potential decrease in participation from current cancer clinical trial investigators due to inadequate funding for this research. This, coupled with the difficulties that exist recruiting patient participants, could have a significant impact on the identification of new therapies and uses of unapproved and newly approved drugs and combinations.

¹ Cancer Clinical Trials: The Basic Workbook. In *National Cancer Institute*. Retrieved June 26, 2006, from http://www.cancer.gov/PDF/091e02f3-5bb9-4ba6-a988-9ad35eab6a61/BasicsWorkbook_m.pdf.

Economics of Cancer Clinical Trials

C-Change sponsored a 2004 survey conducted by The Lewin Group that found financial support for clinical trials varied across institutions and sponsors generally under-funded the actual cost of conducting clinical trials by an average of approximately twenty-five percent.²

Physicians and institutions are facing additional financial and time management challenges that make clinical trial participation more difficult. Financial pressures include reimbursement levels that have not universally kept pace with increasing practice operating costs and competing financial priorities interfere with the ability to integrate clinical trials operations into typical clinical practice settings.

To further compound these challenges, the Federal budget for cancer research has decreased over the past two fiscal years:

- The 2006 budget provided \$31 million less for cancer research than in 2005; and
- The proposed 2007 budget contemplates an additional \$40 million reduction for cancer research.

These cuts may impair the introduction of next generation clinical trials, result in discouraged physician researchers, and undercut required clinical trials infrastructure. Publicly funded clinical trials have consistently been under-funded and only continue because physicians and institutions volunteer individual time and resources to this goal and identify ways to cross-subsidize these efforts.³ The unfunded costs of conducting publicly funded clinical trials are additive to growing physician practice and institutional expenses and are dependent on in-kind contributions of non-compensated staff time as well as other progressively less available practice resources.

Industry funded trials are necessary for the development of new pharmaceuticals; for the most part, publicly funded trials address certain unique and critical issues. For example, publicly funded trials explore topics such as direct comparisons of competing new cancer agents in common diseases, prevention, screening, and quality of life issues. Public funds also spearhead translational research⁴ requiring specimen collections and banking. Industry sponsored trials are important because they are generally successful at identifying new drug treatments that affect large populations and are commercially viable. Publicly funded trials are often the only effective vehicle for assuring continued development of new agents for treatment of additional cancers once that agent has received its initial FDA approval for a single cancer type. The combination of public and private trials is, therefore, necessary to achieve overall progress in cancer treatments.

The recent scientific emphasis on targeted patient specific treatments will require more sophisticated infrastructure in sites in order to more effectively collect, process, store and ship study samples. These additional costs and those required to support centralized data and specimen banks will add to the overall cost of clinical trials as will more sophisticated patient safety monitoring and outcomes measurement systems.

Barriers to Clinical Trial Participation

Despite widespread public acknowledgement of the contribution clinical trials have on the progress in the fight against cancer, barriers to clinical trial participation are increasing. The current low percentage of patients participating in clinical trials can materially extend trial timelines.⁵ Such delays and extensions can lead to increasing costs for study completion and thereby hinder patient access to new therapies, particularly pharmaceutical innovations.

² The Lewin Group. A Guidance Document for Implementing Effective Cancer Clinical Trials, Version 1.2. June 7, 2005. A 2004 Lewin Group study surveyed 13 cancer clinical trial sites. These sites completed a survey regarding the costs and functional requirements associated with cancer clinical trials in addition to their organizations' best practices.

³ This has typically been done by either increasing other profitable services offered and/or by conducting industry sponsored trials at the same sites which more generously reward industry-directed research activity.

⁴ Translational research is designed to facilitate the rapid and effective application of results from research laboratories to patients in clinics – translating clinical developments directly to patient care.

⁵ Grose, M. (April 2, 2005). Recruiting Challenges in U.S. Oncology Trials. In *Applied Clinical Trials*. Retrieved July 5, 2005, from <http://www.actmagazine.com/appliedclinicaltrials>.

Key barriers to the advancement of effective clinical trials are related to:

- Insufficient financial support for publicly funded clinical trials and their infrastructure;
- Constrained and deteriorating finances of physician practice and institutions that limit discretionary spending to internally support trials;
- Shortages of vital manpower in particular sub-specialties and trained physician researchers;
- Limited participation in cancer clinical trials by both clinicians and patients, including minority populations;
- Lack of awareness or priority placed on importance of clinical trial participation on the part of physicians, policy makers and patients;
- Reduced numbers of medical resident participants in hematology and oncology⁶, resulting in a decrease in the number of oncologists proportionate to increased patient demand; and,
- Complex and sometimes inefficient or overlapping regulatory requirements that impose burdensome financial and personnel requirements.

In summary, the current level of public monies dedicated to cancer clinical trials and the requisite infrastructure cannot accommodate the current, let alone changing paradigm of cancer treatment development. Where earlier clinical treatments such as chemotherapy were often effective at arresting disease processes, promising innovations are now paving the road for more highly targeted cancer treatments and personalized medicine without risking potentially negative impacts on patients who may not benefit from toxic treatments. Public funding commitments to cancer trials are diminishing and threaten the viability and sustainability of future research in this direction.

To ensure the success of cancer clinical trials, it is essential to increase the number of patient and physician participants as well as invest in the clinical trial infrastructure needed to support rapid breakthroughs in the new biology of cancer care. The current public policy concern is that insufficient funding cannot support either the new biology of cancer care or the complexities of the infrastructure required to support it.

⁶ There was a decrease in the number of available residency positions for hematology and hematology/oncology from the 03-04 to the 04-05 academic year from 1377 to 1300 nationally. In the same time frame, the number of resident slots filled for these subspecialties increased from 1166 to 1208. The percentage of filled slots decreased by only 2% between these periods. Source: ACGME Resident Population by Specialty, www.acgme.org as viewed on June 26, 2006

Introduction: Purpose and Overview

A. Purpose

The primary purpose of this document is to improve policy makers' and other stakeholders' understanding of the process, economics and barriers related to cancer clinical trials. These barriers will continue to hinder this nation's ability to introduce new and effective cancer therapies and improve cancer prevention. This document also highlights the necessity of adequate and sustainable public funding to ensure increased participation and effective clinical trial processes. It is hoped that an increased understanding and discussion about the importance of effective clinical trials will serve to increase their visibility and the substantial complexities involved in participation for physicians and cancer patients throughout the country.

In order to address the issues that most affect the current state of cancer clinical trials, this policy document will review the following topics:

- Current cancer clinical trial environment;
- Economics of cancer clinical trials;
- Regulatory environment of cancer clinical trials; and
- Barriers to clinical trial participation.

B. Overview

Today, approximately 8 million Americans are living with, or surviving, cancer, and approximately 4.67 percent of all health care expenditures were dedicated to cancer treatment (totaling \$72 billion) in 2004.^{7,8} In 2006, the American Cancer Society projected approximately 1.4 million new cancer diagnoses per year.⁹ However, the Federal budget for cancer research has decreased over the past two fiscal years. In 2006, Federal funds provided \$31 million less for cancer research than in 2005 and the proposed 2007 budget indicates an additional \$40 million reduction in cancer research. This trend has resulted in industry-wide concerns such as those expressed by the American Association for Cancer Research: "the cancer research community is bracing for a major shift in the number of scientists in the field and, consequently, the speed of advances needed to prevent and cure this disease."¹⁰

Despite the robust number of new or emerging cancer therapies – nearly 400 drugs currently available for testing in the most recent report from Pharmaceutical Research and Manufacturers of America (PhRMA) - there has not been a corresponding increase in clinical trial participation rates.¹¹ According to the National Cancer Institute (NCI) "we will never know the true effectiveness of a cancer treatment or a way to prevent cancer unless more people are involved in clinical trials." Today's most effective cancer treatments began as clinical trials and are based on previous trial results, yet only three percent of US adults with cancer currently participate in clinical trials – already "far fewer than the number needed to answer the most pressing cancer questions quickly."¹² The NCI, the CCG, and many other organizations, have worked to increase the public's awareness and understanding of the importance of participation in clinical trials.

⁷ Just the Facts. In *U.S. Food and Drug Administration*. Retrieved April 14, 2006, from www.fda.gov.

⁸ The Cost of Cancer. In *National Cancer Institute, Financial Management Branch*. Retrieved April 25, 2006, from <http://fmb.cancer.gov/statistics/C-3.pdf>.

⁹ Cancer Facts & Figures, 2006. In *American Cancer Society*. Retrieved April 14, 2006, from <http://www.cancer.org/downloads/STT/CAFF2006PWSecured.pdf>.

¹⁰ Funding for, and Societal Impact of, Cancer Research to be Discussed. In *American Association for Cancer Research*. Retrieved March 28, 2006, from <http://www.aacr.org>.

¹¹ 2005 Survey: Medicines in Development for Cancer. In *PhRMA*. Retrieved August 28, 2006, from <http://www.phrma.org/files/Cancer%20Survey.pdf>.

¹² Cancer Clinical Trials: The Basic Workbook. In *National Cancer Institute*. Retrieved June 26, 2006, from http://www.cancer.gov/PDF/091e02f3-5bb9-4ba6-a988-9ad35eab6a61/BasicWorkbook_m.pdf.

There are more cancer survivors in the U.S. health care system than ever before (over 10 million). "Of this growing population of survivors, 1.5 million were diagnosed more than 20 years ago. This achievement is a direct result of clinical trial research producing more effective methods of prevention, detection, and treatment. The Coalition of Cancer Cooperative Groups estimates that nearly 200,000 newly diagnosed patients each year may be clinically eligible to participate in a cancer treatment trial; currently only about 50,000 patients participate a year."¹³ A recent survey found that only 10% of cancer patients recalled being aware at the time of their diagnosis that a cancer clinical trial might have been a treatment option. The same study found that 73% of patients cited their physician as their source of awareness.¹⁴

One of the key barriers limiting patient participation is the relatively small number of practicing oncologists who actively participate in clinical trials. The time and financial resources required to participate in clinical trials might constitute a material barrier for wide community physician participation in such activities. Given the increasing financial pressures on physician practices and health care institutions, it is becoming more likely that the financial means to participate in clinical trials will decrease.

In addition, the number of new physicians choosing to specialize in oncology is not increasing apace the predicted demand for oncology services. The resultant workloads encountered by existing investigative sites may further pressure those physicians to place less emphasis on clinical trials participation, or choose not to participate any longer. This reduction in human capital is exacerbated by a concomitant decrease in discretionary funds available to community hospitals and even larger centers due to rising medical costs in general. The decrement in both physician participation rates and funding from both government and private sources comes at a time when available new treatments that require testing in oncology have never been greater.

Prior to approval by the FDA, cancer drugs typically undergo three phases of human testing. Following FDA approval some cancer drugs are required to undergo a fourth phase of human testing where a drug's long-term effects are determined. These four phases of cancer clinical trials each involve a different focus and different numbers of study participants.

The performance of clinical trials is a vital component of FDA's drug approval process, without which advances in cancer therapeutics would not be possible. Ultimately, increased participation in clinical trials "reduces the time it takes for researchers to enroll participants in trials and complete them - and speeds the movement of new drugs or treatments into standard care."¹⁵

According to the FDA, from January 2005 through April 2006, eleven new cancer drugs were approved for treatment use. This count includes new dosages, new indications and new administrations of previously-approved compounds.¹⁶ Often the lengthiest aspect of the drug approval process is "finding the people to participate in each trial phase."¹⁷ A critical amount of quality trial data is required prior to FDA submission and without sufficient willing patients and investigators, the drugs will not be approved.

Advances in cancer care and the development of cancer therapeutics depends largely upon an effective clinical trial process. The clinical trials process depends, in turn, on sufficient funding to allow access to clinical trials in a broad array of clinical settings to assure participation by patients and investigators. Delays caused by difficulties in recruiting participants, when combined with potential decreases in participation on the part of current clinical trial investigators, could have a significant impact on the identification of new therapies and uses for unapproved and approved drugs and combinations.

¹³ The Lewin Group. A Guidance Document for Implementing Effective Cancer Clinical Trials, Version 1.2. June 7, 2005.

¹⁴ Hede, K. "Research Foundations Find Strength in Numbers." *J Natl Cancer Inst* 2006; 98: 572-574.

¹⁵ The Lewin Group. A Guidance Document for Implementing Effective Cancer Clinical Trials, Version 1.2. June 7, 2005.

¹⁶ List of Approved Oncology Drugs with Approved Indications. In *U.S. Food and Drug Administration*. Retrieved April 25, 2006, from <http://accessdata.fda.gov/scripts/cder/onctools/druglist.cfm>.

¹⁷ Cancer Clinical Trials: The Basic Workbook. In *National Cancer Institute*. Retrieved June 26, 2006, from http://www.cancer.gov/PDF/091e02f3-5bb9-4ba6-a988-9ad35eab6a61/BasicWorkbook_m.pdf.

The FDA developed two mechanisms to make new drugs available to patients more quickly: accelerated approval and the designation of priority drugs. As a result, the FDA has accelerated the approval process for some cancer drugs and now assists study sponsors in the design of more efficient clinical trials.

Regardless of the processes in place to assist in the efficient execution of clinical trials, adequate funding and an awareness of the mechanisms of clinical trials are critical to ensure (1) physicians invest the time and staff appropriate for conducting clinical trials; and (2) patients are able to learn about and consider participation in cancer clinical trials. The longer it takes to train physicians and enroll appropriate study subjects, the longer it takes for effective drugs to be approved. An increase in clinical trial participation by both doctors and patients in effective and publicly reported clinical trials, resulting in strong data collection and accurate results, will further promote and facilitate cancer research and ultimately cancer care. However, current trends in physician reimbursement and the decreasing availability of sub-specialists proportionate to patient demand do not support an overall increase in clinical trial participation. The current trend in cancer clinical trial participation by cancer patients results in trial timeline lengthening by months or years.¹⁸

I. Current Clinical Trial Environment

A. Cancer Clinical Trial Statistics

There are 4,970 cancer clinical trials underway in the United States for the diagnosis, prevention, treatment and management of symptoms of cancer.¹⁹ An estimated 3,200 of these studies pertain to the treatment of cancer, and of those, 1,405, or 44 percent, are supported by federal funding through the NCI.²⁰ Remaining trials are supported by a number of different private organizations such as pharmaceutical companies, academic institutions, private foundations, and single investigators.

A recent analysis shows that cancer cooperative groups account for approximately 85% of the NCI sponsored cancer clinical trials accruals.²¹ This study analyzed accrual onto NCI sponsored cancer clinical trials from January 2003 through June 2005 where approximately 70,000 patients were entered into clinical trials during that time frame. Sixty-three percent of NCI sponsored cooperative group trials are large phase III trials. It should be noted, and will be discussed below, that the participation of community based practices is an essential component of this system; community based practices accounted for 64% of entries onto cooperative groups studies during that time period. The NCI sponsored Cancer Centers, and other networks and research consortia, entered approximately 15% of patients onto clinical trials during that same time frame. Ninety-eight percent of these entries were onto early phase clinical trials (phase I-II studies). Cancer drug development performed in the publicly funded system is an enterprise which capitalizes on the strength of both the academic and community based strengths within the system.

B. Trial Selection and Start-Up Costs

There was a large difference in the number of phase II and phase III trials reported as “open” in academic medical centers compared to non-academic medical centers. For example, the Lewin Group’s 2004 survey found that the median number of open trials for an academic medical center was 121. Non-academic medical centers reported approximately half the number of open clinical trials, and a majority of the trials were publicly funded by agencies such as the NCI and NIH. The remainder of these trials were privately sponsored. Similar to academic medical centers, non-academic medical centers reported far more open publicly sponsored trials, compared to industry sponsored trials.

¹⁸ Grose, M. (April 2, 2005). Recruiting Challenges in U.S. Oncology Trials. In *Applied Clinical Trials*. Retrieved July 5, 2005, from <http://www.actmagazine.com/appliedclinicaltrials>.

¹⁹ Coalition of Cooperative Groups Press Release. Most Cancer Patients Satisfied with Clinical Trial Experience, Yet, Few Aware of Opportunity: Study Shows Improved Physician-patient Communication Could Increase Enrollment in Cancer Clinical Trials. June 5, 2006.

²⁰ These figures are available in NCI’s PDQ database.

²¹ Coalition of Cancer Cooperative Groups. Baseline Study of Patient Accrual Onto Publicly Sponsored U.S. Cancer Clinical Trials: An Analysis Conducted for the Global Access Project of the National Patient Advocate Foundation. Philadelphia, PA: Coalition of Cancer Cooperative Groups; February 2006.

There are many factors that influence the ability or decision of a clinical trial site or investigator to open a particular study. Internal resources, such as time available to dedicate to research (a portion which may be unfunded), the research infrastructure including staff and patient base all influence how physicians choose studies. The types of studies chosen also vary by the type of research center. Community physicians tend to open trials across tumor types and stages, while academicians open trials generally related to their oncology specialty. A difference in the types of patients being studied is also true for cooperative group versus non-cooperative group trials. For instance about 46% of cooperative group trials are directed toward patients with localized disease, whereas about 85% of trials performed in the Cancer Center/academic setting are directed toward patients with advanced metastatic disease. As noted above, community based investigators who participate actively in the cooperative group structure are essential in the performance of those studies in localized disease, generally in the adjuvant setting.

Start-up costs for clinical trials are typically high for several cost categories including staff training, Institutional Review Board (IRB) approval, and overall staff time for start-up visits and form completion. Start up costs generally include site regulatory approval, site training and time for reviews. Opening multiple trials for many patient types can deliver efficiencies and economics of scale and facilitate a potentially larger breadth of research.

C. Changing Nature of the Science

In 2003, the NIH created a “roadmap” for medical research in the 21st century. This roadmap contains three primary themes bridging medical research across each institution within the NIH, including the NCI. These three themes include:

- New pathways to discovery – to advance our understanding of biological systems and to build a better toolbox for medical research;
- Research teams of the future-to stimulate new ways of combining skills and disciplines in the physician, biological, and social sciences to realize the great promise of medical research; and
- Re-engineering the clinical research enterprise-to contribute to accelerating and strengthening clinical research by adopting a systematic infrastructure that will better serve the evolving field of scientific discovery.²²

Consistent with the added focus on translational research, there appears to be a shift in focus toward community hospitals and oncology practices increasing their involvement in clinical trials and other research efforts. The renewed community interest in research has not necessarily been accompanied by any material change in the current training and funding opportunities provided to potential community based investigators. New community-based investigators will need training in research methods and processes to facilitate their participation.

The nature of cancer clinical trials is changing as researchers discover more about the genetic determinants of cancer at the molecular level and begin to recognize the need to develop an even stronger research system that “integrates the individually strong components of the current system into a cross-disciplinary, scientifically-driven, cooperative research effort.”²³

This translational research is designed to facilitate the rapid and effective application of results from research laboratories to patients in clinics – translating clinical developments directly to patient care. This research could further accelerate the discovery of new treatments and drugs targeted to individual patients and help identify deficiencies in existing therapies. The rapid pace of scientific progress, including, but not limited to, molecular technology, has created an ever-increasing number of novel therapies to test. If managed and funded effectively, translational research will result in the development of more effective personalized cancer care.

The emerging use of molecular biology “may herald an era in which physicians no longer make treatment choices that are based on population-based statistics but rather on the specific characteristics of individual patients and their tumor...”²⁴ Translational research requires that scientists in laboratories, traditional medical researchers, and

²² NIH Roadmap for Medical Research. In *Office of Portfolio Analysis and Strategic Initiatives*. Retrieved July 6, 2006, from <http://nihroadmap.nih.gov/index.asp>.

²³ Clinical Trials Working Group. Restructuring the National Cancer Clinical Trials Enterprise. National Cancer Advisory Board. June 2005.

²⁴ Dalton WS, et al. An Invitation to the Table. *Science*, May 2006; 312 (26): 1165-1168.

biostatisticians collaborate far more closely with community oncologists in clinical trials to further pursue developments in molecular biology. The collection, reporting and management of specific tumor and tissue samples and their characteristics will become a more frequent and significant component of clinical trial research requiring the support of increasingly sophisticated tissue and data repositories.²⁵ This expanded approach will require a crossing of traditional lines between basic population and laboratory-based research and the work done by community oncologists. It will necessitate far greater collaboration among multiple sectors and diverse health care professionals as well as a level of comprehensive sharing of information that has not previously occurred.

At the NCI, the Clinical Trials Working Group of the National Cancer Advisory Board was established to lead a "Restructuring of the National Cancer Clinical Trials Enterprise". This group has been tasked with identifying how to redesign the clinical trials environment so that it is "...not only more efficient and coordinated but founded on the best science. 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 investigators aligned in a new kind of multi-disciplinary, scientifically-driven, cooperative research endeavor."²⁶

Despite the efforts of many in the oncology community and the strategic orientation of the NCI, the public funding currently in place is not adequate to support the tasks as outlined in such a way as to ensure progress in cancer research given the challenges of the new science. The next section reviews the economics of cancer clinical trials to provide more perspective on the challenges faced in advancing cancer research.

II. Economics of Cancer Clinical Trials

The previous Lewin study found that publicly funded clinical trials reimburse at approximately \$2,000 per study subject (*Exhibit 1*). Including private sponsor reimbursement for cancer clinical trials, the average revenue per subject was approximately \$2,676. In this same study the randomized phase II publicly sponsored study median cost, including labor and overhead, was \$6,266, and the phase III median cost was \$3,427. Thus, the total cost of the studies for more than three-quarters of sites is not fully covered by trial sponsors.

Exhibit 1: Reported Study Cost per Subject including Labor and Overhead for Sample Randomized Phase II and III Studies

Reported Study Cost per Subject					
Randomized		Per Subject Reimbursement	Median	25 th Percentile	75 th Percentile
Phase II	Publicly Sponsored	\$2,000	\$6,266	\$3,618	\$9,001
	Privately Sponsored	Variable	\$8,450	\$4,713	\$9,473
Phase III	Publicly Sponsored	\$2,000	\$3,427	\$1,966	\$6,950
	Privately Sponsored	Variable	\$4,696	\$2,532	\$9,850

The Lewin Group's study found that median revenue per subject varied both by trial sponsor and clinical trial site. As we noted earlier, public reimbursement does not generally cover the entire cost of conducting cancer clinical trials.²⁷ Thus, there is no financial incentive to participate in publicly funded trials. Considered individually, industry sponsored trials generally cover research costs for clinical trials they initiate.

²⁵ Given that these repositories will be used for multiple studies across many types of clinical trials, they are unlikely to be supported by industry and will depend on significant investments of public monies to be established and/or maintained.

²⁶ Clinical Trials Working Group. Restructuring the National Cancer Clinical Trials Enterprise. National Cancer Advisory Board. June 2005.

²⁷ Plans and Priorities for Cancer Research. (2003). In *National Cancer Institute*. Retrieved July 6, 2006, from <http://plan2003.cancer.gov>.

A. Publicly Funded Cancer Clinical Trials

In 2004, the NCI spent approximately \$800 million on cancer clinical trials and the most recent estimate produced by PhRMA indicates that approximately 400 cancer medicines are either in clinical trials or under FDA review waiting for approval.²⁸ There are burgeoning numbers of new compounds to be tested and demand for trials has been increasing, however, participation has not.

The NCI funds multiple types of clinical research programs including:

- Clinical Trial Cooperative Groups: networks of researchers and institutions organized according to region or medical specialty that collaborate to conduct large-scale, multi-site clinical trials often involving thousands of patients.
- Clinical Cancer Centers and Comprehensive Cancer Centers: major academic and research institutions characterized by scientific excellence that sustain broad-based interdisciplinary programs in cancer research.
- Specialized Programs of Research Excellence (SPOREs): cross-cutting scientists and clinical researchers at select academic sites that focus on translating laboratory discoveries into useful clinical approaches for the diagnosis, treatment and prevention of specific cancers.
- Community Clinical Oncology Programs (CCOPs) and Research Bases: smaller-scale, community-based medical facilities and individual physicians who join together to leverage infrastructure and other trials-related activities to take better advantage of participating in treatment, cancer control and prevention studies implemented by their Research Bases.
- Investigator initiated research grants from academic sites usually focused on smaller phase I and II trials.
- Contract and grant-related clinical trials consortia in which selected academic sites and their affiliate networks develop new drugs for cancer treatment and prevention.

B. Privately Funded Cancer Clinical Trials

Estimating the development costs associated with new cancer therapies and their associated clinical trials is difficult. These difficulties result, in part, from pharmaceutical compound patents developed in a competitive and proprietary environment within the pharmaceutical industry. The exact dollar amount spent on cancer clinical trials by the industry is unknown. A recent estimate from PhRMA suggests that the entire biopharmaceutical industry spent approximately \$51.3 billion on research and development,²⁹ but the actual amount spent in cancer drug development and approval was not delineated. However, we do know that more than 400 drugs are currently available for testing.

Pharmaceutical sponsors conduct research for drug development and approval. Studies vary in complexity from phase I to phase III and study management costs, including investigator grants, account for much of the research and development costs. In oncology, drug approval is only the first step; adjacent to studies done to support an application for approval are studies supported for further exploratory development across multiple tumor types. Much of that research is publicly funded.

Private organizations sponsor trials including the American Cancer Society, the Susan G. Komen Foundation, the Avon Foundation, and others; although, these private sources comprise a small proportion of total private sponsorship.

C. Study Sites and Investigator Resources

The resources required to comply with applicable regulations governing clinical trials conduct vary by research site, study design, and reimbursement available. These three variables are interrelated and together influence how and where clinical trials are conducted.

²⁸ NCI-Supported Cancer Clinical Trials: Facts and Figures. In *National Cancer Institute*. Retrieved April 16, 2006, from <http://www.cancer.gov/clinicaltrials/facts-and-figures>.

²⁹ Pharmaceutical Industry Profile 2006. In *PhRMA*. Retrieved April 14, 2006, from <http://www.phrma.org/files/2006%20Industry%20Profile.pdf#search=%22pharmaceutical%20industry%20profile%22>.

1. Research Sites

Clinical research settings include physician offices, cancer centers, other medical centers, community hospitals and clinics, university medical centers, and veterans' and military hospitals.³⁰

Each research setting offers different resources. For example, an academic facility may have a full study support team that includes pharmacy, laboratory and pathology as well as a research coordinator, and budgeting support. A private practice setting might be limited to a part-time staff member supporting research activities requiring that the investigator perform the other clinical trial support functions needed; regardless of a site's size or internal resources. The quality of the infrastructure, personnel and fiscal resources all impact study selection. The costs of drug development and related costs of clinical trials at different sites are not transparent, rendering the cost of clinical trials at any given site difficult to assess.

The next section of this report details additional factors that may contribute to a highly complex economic environment for clinical trials.

2. Study Design

Although treatment trials are the most common and necessary trials for new drug development, other types of studies are supported by the NCI. NCI supports six primary types of trials - treatment, prevention, screening, diagnostic, quality of life, and genetics trials.

The scientific design of a study, and the phase of drug development, impact the complexity of a study and govern the ability of a particular investigator to participate. There are four phases of clinical cancer trials:

- Phase I: Determine the side effects and appropriate dosage of a new drug. Generally involves a limited number of study sites, due to the strict patient monitoring and consistency needed during the study. Most often at academic centers where infrastructure can support monitoring and patient sample collection.
- Phase II: Define potential effectiveness of a new drug. Generally performed at more sites, but sites are often selected for their ability to collect safety and efficacy measurements required for the study.
- Phase III: Compare effectiveness of the new treatment to the best available treatment. Conducted at a large number of study sites, and since the agent has been widely studied, more safety information is available.
- Phase IV: After FDA approval and marketing, a drug can be further evaluated for side effects that were not apparent in earlier trials. Thousands of patients can be enrolled in these trials that are becoming increasingly common to ensure long-term safety and efficacy.³¹

3. Reimbursement and Site Funding

The type of reimbursement for study sites varies by study sponsor. There are generally two types of trials: pharmaceutical sponsored studies and non-pharmaceutical sponsored studies. Non-pharmaceutical sponsored studies include investigator /institution sponsored studies, network or other consortia sponsored studies, and publicly sponsored studies. Studies that are not sponsored by manufacturers may be afforded additional support including the study drug or placebo and other funding for study-specific operational costs. Such funds can be used to support study specific tests, pharmacogenomic testing, and costs not covered by standard of care and reimbursement guidelines.

Payments to study sites for specific trials are contractual with the sponsor. Payments are typically based on patient accrual (the number of patients participating) and adherence to specific clinical practice guidelines and regulations. While pharmaceutical companies can adjust study site budgets based on study complexity, publicly funded research is typically reimbursed at a fixed rate, currently \$2000. This number has not kept pace with inflation. Consequently, investigators and institutions, when possible, supplement clinical trial costs from clinical activities or from other sources including other operating funds, grants, gifts and other philanthropic sources.

³⁰ Ibid.

³¹ National Cancer Institute. National Cancer Institute Fact Sheet: Clinical Trials: Questions and Answers.

If the public budget that supports cancer research remains flat, the reimbursement for accruals is likely to remain low and there could be a material decrease in the number of willing physician investigators for publicly funded trials.

There are unique and important topics explored through publicly funded clinical trials including direct comparisons of competing new cancer agents; tests of new agents for uncommon diseases; clinical trials that require specimen collections or translational research; and quality of life and assessments of the cost of different treatment regimens (pharmacoeconomics). Privately sponsored trials are successful at identifying new, commercially viable drug treatments that affect large populations. Publicly funded trials have resulted in significant contributions to the advancement of cancer treatment, and are often the only effective vehicle for assuring continued development of new agents for treatment once an agent has received FDA approval for a specific cancer type. The combination of public and private trials is necessary to achieve comprehensive progress in cancer treatments; the unique contributions of publicly funded trials, therefore need to be acknowledged and protected.

D. Issues with Publicly Funded Trials

A review of literature for costs of clinical trials showed that average non-labor costs for a phase II or phase III therapeutic treatment trial have been reported between \$3,091 and \$6,094 per study subject. These studies report large variation in per subject costs that range from approximately \$2,000 per study subject to more than \$19,000 per study subject. The total study cost calculations from the respondents of \$1,966 to \$9,849 are within reported ranges found in the currently available literature.³²

The Lewin Group's study found that median per subject reimbursement varied both by trial sponsor and clinical trial site. On average per subject reimbursement was approximately \$2,676. As we noted earlier, Federal reimbursement does not generally cover the entire cost of conducting cancer clinical trials.³³

Although most frequently contingent on patient milestones, there are certain publicly funded trials that provide an initial start-up payment to a clinical trial site. There are advantages and disadvantages to providing payments upfront. For example, if the trial fails to accrue subjects, the trial sponsor realizes no value for its investment. Absent such advance payment, the incentive to invest staff and resources in speculative but promising clinical trials is low. The NCI sponsored Cooperative Groups account for approximately 85% of patients who enter NCI sponsored trials. About 65% of patients entered onto these trials are entered through community based practices.³⁴ There are two categories of community participation: 1) community practices which are affiliated with academic or large hospital programs—funded on a per-case reimbursement basis, and 2) community clinical oncology programs (CCOPs) which are funded on a grant basis. In both instances, community practices are significantly under-funded. As noted previously, the per-case reimbursement system is well below what is required to cover the research costs, and in the current NCI funding environment, the CCOPs grant system with its capped dollar amount is a disincentive to accrual, since the more patients who are entered into studies, the less overall research reimbursement occurs. Without continued active community based participation, the major accrual source for large phase III trials will be in jeopardy.

Academic based practices have similar clinical trials research funding structure: i.e., through a case reimbursement approach or grant funded approach which is essentially capped in the current restricted budgetary environment, regardless of whether they are performing cooperative groups trials or those funded through other NCI grant mechanisms. Regardless of how the reimbursement for publicly funded cancer clinical trials occurs, whether grant based or case based, it is generally not sufficient to cover investigator costs and may result in a disincentive for physicians to participate or encourage patient participation in clinical trials programs. Furthermore, possible Medicare reductions in the coverage of basic clinical services provided to clinical trial participants may cause concern among clinical trial investigators given that public trials are already under-funded.

³² Emanuel, E.J. The Cost of Conducting Clinical Research. *Journal of Clinical Oncology* 2003; 21(22)

³³ Plans and Priorities for Cancer Research. (2003). In *National Cancer Institute*. Retrieved July 6, 2006, from <http://plan2003.cancer.gov>.

³⁴ Hede, K. "Research Foundations Find Strength in Numbers." *J Natl Cancer Inst* 2006; 98: 572-574.

ASCO established a series of standards for clinical trial Medicare coverage.³⁵ The goal of the ASCO standards is to provide a model for state and private insurance programs including Medicaid, managed care, and private insurance plans for covering patients enrolled in phase I through phase IV clinical trials.

In an attempt to address these reimbursement issues associated with clinical trial participation, policy makers have passed state-level legislative mandates or other arrangements with large health plans to ensure reimbursement of routine medical costs for trial participants. A 2004 study reported in the *Journal of the National Cancer Institute* examined whether these policies ensure coverage for such services for trial participants. That study concluded “state coverage policies related to clinical trials were associated with statistically significant increase in phase II cancer trial participation and did not increase phase III cancer trial enrollment.”³⁶

III. Regulated Environment of Cancer Clinical Trials

A. Regulatory Overview

Good clinical practices is a term used within the health care community that references federal regulations describing the responsibilities of all parties involved in the conduct of clinical research on human subjects. The regulations are critical for ensuring accurate scientific results and providing protection for participants’ safety and well-being. Principal investigators are obligated to comply with the Code of Federal Regulations (CFR) pertaining to the protection of human subjects involved in research originating from two separate agencies within the Department of Health and Human Services (HHS). These regulations are sometimes conflicting and/or redundant.

The HHS regulations (45 CFR 46) apply to research involving human subjects, conducted by the HHS or supported in whole or in part by the HHS (including the NCI). Enforcement of these regulations is the responsibility of the Office of Human Research Protection (OHRP). The FDA regulations (21 CFR 50 and 56) apply to research involving products regulated by the FDA—federal funds do not need to be involved. Enforcement of these regulations is the responsibility of the Bioresearch Monitoring Branch of FDA. When research involving products regulated by the FDA is publicly funded, investigators must comply with both the HHS and FDA regulations. While these regulations are basically similar, there are some distinct differences about which the investigators must be aware.

Federal regulations protect the rights of human subjects and prescribe clinical trial staff responsibilities. However, the infrastructure and principles of regulatory practices were established over 30 years ago when the majority of trials were conducted by a single investigator at one institution with local participants. In today’s environment, single-investigator trials are still conducted, however, many trials are carried out in multiple research sites across the country. The regulatory requirements remain in place for all clinical investigators, regardless of the degree to which an investigator (such as a community oncologist) has been involved in the clinical trial’s protocol development or the volume of patients accrued to a particular community practice. The nature of clinical trials has changed inviting increased involvement of community oncologists whose clinical and research activities are blended, sometimes indistinguishably, into the community practice environment. Practicing community physicians also choosing to participate in clinical trials are also subject to the same regulatory requirements as large research institutions with long-established and typically comprehensive research administrative systems.

Other regulatory challenges include responding to the shift toward large style community based clinical trials, dealing with cumbersome adverse event reporting requirements, and the impact of global research requirements from international clinical trials. These challenges are detailed in the following sections.

1. Shift to Multi-center Consortia

“Today, biomedical research is conducted by multi-center consortia comprised of thousands of investigators and participants at research sites located across the nation and even the world.”³⁷ It is not unusual for an investigator at a single site to have fewer than 10 participants accrued to any particular trial. The Cancer Summit workgroup on regulatory issues concluded at their eighth summit meeting: “. . .the governing regulations mandating the local review process for HSP [human subject protection] has failed to adapt to this change in the research enterprise resulting in an overburdened and inefficient system. . . To this end, the review process for multi-center trials must be streamlined.”³⁸

Prior to investigator participation in cancer clinical trials, the institution and staff must have an understanding of these regulations and meet lists of complex requirements including the operations of an Internal Review Board (IRB) and the review of clinical trial protocols. Granting agencies such as the NIH and NCI will only make awards for research involving human subjects when the study protocols have been reviewed and approved by an IRB. Local IRBs can unnecessarily duplicate the work of other regional IRBs established in order to ensure they each meet Federal requirements. These regulatory requirements necessitate a significant financial investment on behalf of a potential clinical trial site well in advance of accruing the first patient into a clinical trial. Sites choosing to participate in publicly sponsored trials must comply with the codified regulations originating from multiple Federal agencies including those set forth by the FDA and the Office of Human Resource Protection (OHRP) as well as the NIH, and, where applicable, those of the International Conference on Harmonisation.³⁹

A number of organizations, including ASCO and the Cancer Summit, have proposed restructuring the local human subject protections process, and the IRBs in particular, to minimize the procedural requirements involving pre-trial review to eliminate redundancies and reduce start-up time and costs for new trials while maintaining human subject protection. ASCO published a public policy statement recommending centralized trial reviews to eliminate many time-consuming aspects of the IRBs.⁴⁰ This policy statement was developed close to a pilot initiative from the NCI establishing a central IRB (CIRB). The NCI’s CIRBs are now available as alternatives to some local IRBs for investigators who want to streamline the administrative process by delegating certain required tasks to an approved CIRB and still meet human protection requirements.⁴¹ While the CIRBs offer relief for certain investigators with limited infrastructure, they cannot replace the more sophisticated and well-established IRBs at major institutions throughout the country. The Cancer Summit’s Workgroup on regulatory issues noted, “. . .the burden placed on both the investigator and the individuals designated to provide oversight of research is cited by many would-be investigators and institutions as a reason for their decision to be a non-participant.”⁴²

Multiple stakeholders have raised concerns about the overlapping roles and functions of IRBs in the clinical trial process – a longstanding problem for IRBs. As highlighted by the AAMC, there is a lack of harmony between “the regulatory and policy requirements of various HHS and other federal agencies for the reporting of unanticipated problems and adverse events; the same is true for human research protection regulations more broadly.”⁴³

³⁷ Cancer Summit Series on Cancer Clinical Trials. Workgroup 6 Report: Changing Paradigms: Impact of the Local Regulatory Process on Participation in Clinical Trials, Summit VIII-Retooling the System: Accelerating Solutions. September 20, 2004.

³⁸ Ibid.

³⁹ The International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice and Clinical Safety and Data Management. This Conference has established international guidelines for clinical trial research that must be met when clinical trial protocol are being used beyond the United States. These guidelines are different than those newly promulgated by the European Union mentioned below.

⁴⁰ American Society of Clinical Oncology Policy Statement: Oversight of Clinical Research, Adopted on November 7, 2002. *Journal of Clinical Oncology*, June 15, 2003; 21 (12).

⁴¹ The NCI established the first adult CIRB in 2001 and pediatric CIRB in 2004. The timeframe for this pilot program has been extended after its initial pilot period given its initial success.

⁴² Cancer Summit Series on Cancer Clinical Trials. Workgroup 6 Report: Changing Paradigms: Impact of the Local Regulatory Process on Participation in Clinical Trials, Summit VIII-Retooling the System: Accelerating Solutions. September 20, 2004.

⁴³ Letter from Jordan G. Cohen, MD, president of the Association of Medical Colleges, to the Office of Human Research Protections concerning the October 1, 2005 Draft Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others. January 11, 2006.

³⁵ Coverage of Routine Patient Care Costs in Clinical Trials. Position Statement. American Society of Clinical Oncology; March 2005.

³⁶ Gross, C.P. et al. Cancer Trial Enrollment After State-Mandated Reimbursement. *J Natl Cancer Inst* 2004;96: 1063-1069.

In January, 2006, the FDA announced new guidelines to streamline clinical research for new medical treatments. These new guidelines were “enthusiastically” supported by the American Association for Cancer Research, and specifically targeted streamlining clinical research in its earliest phases.⁴⁴ These guidelines represent progress toward streamlining clinical trial processes. As we discuss below, the need for further regulatory streamlining for the later phases of research as well as IRB responsibilities remains.

2. A Regulatory Challenge – Adverse Event Reporting

Evaluating the severity and frequency of adverse events can be crucial to determining the balance between the agent’s safety and efficacy. Reporting adverse events is, therefore, an important component of the clinical trials process. A procedure for ongoing review of suspected adverse drug reactions that occur during the conduct of clinical trials is also a critical aspect to minimize risk to participants.

Multiple parties have responsibilities in a clinical trial to identify, evaluate, report and analyze adverse events, including clinical investigators, sponsors, the FDA, Data Monitoring Committees (for large phase III trials) and IRBs. In early 2005, the FDA held a public hearing requesting stakeholders’ guidance to address concerns related to adverse events reporting.

FDA is increasingly aware of concerns within the IRB community that the process is burdensome, inefficient and not as effective as it should be... FDA highlights two main reasons for the current situation. Compared with when IRB regulations were initially introduced, there are more clinical trials and a larger number of big multi-center studies. Both developments have increased the numbers of adverse events with which IRBs must contend. Second, the adverse event reports generally do not contain adequate information and are not organized in a way that makes it easy to track adverse event trends...⁴⁵

The FDA has since published guidance for IRBs, investigators and sponsors and a proposed rule on IRBs to begin to address concerns related to modernizing adverse event reporting in a multi-center trial environment. The FDA Deputy Commissioner for Operations is leading a steering committee to strengthen the FDA’s approach to bioresearch monitoring among other regulatory issues as part of its Critical Path Initiative.⁴⁶ The Federal Office of Human Research Protection (OHRP) requested public comment on the draft guidance it issued in October 2005 on the reporting and review of adverse events in research. Investigators, sponsors and other key stakeholders were asked to submit comments by early 2006. This guidance was intended to be the first among several promised initiatives directed at developing a more comprehensive and harmonized approach to monitoring of safety information during clinical research.

3. Impact of Global Research Environment

In addition to the range of US regulatory requirements, investigators and clinical trial research sites are also faced with additional demands from project sponsors (generally pharmaceutical companies) conducting clinical trials internationally. The European Union recently adopted more extensive clinical trial directives than existing US standards. The pharmaceutical companies operating in a global market are working to harmonize their administrative requirements in the context of international clinical trials activities. The new range of international regulatory requirements adds pressure to investigators participating in industry-sponsored trials to acknowledge and implement a new and different set of clinical trials processes that are, in some cases, different from current practice. The development of a global framework for research might stimulate a more effective clinical trials process. In the interim, the burden of potentially duplicative reporting and administrative procedures could make participation in clinical trials less appealing to current investigators and inhibit new investigators’ participation.

⁴⁴ AACR Supports New FDA Clinical Research Guidelines. (January 12, 2006). In *American Association for Cancer Research*. Retrieved July 6, 2006, from <http://www.aacr.org>.

⁴⁵ Clinical Trial Adverse Event Reporting Improvements to Be Discussed at March Meeting, FDA Advisory Committee.com, The Pink Sheet as posted February 11, 2005.

⁴⁶ FDA News Release: FDA Announces New Initiatives to Modernize the Regulation of Clinical Trials and Bioresearch Monitoring. (June 26, 2006). In *U.S. Food and Drug Administration*. Retrieved August 9, 2006, from <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01396.html>.

B. Regulatory Impact on Clinical Trial Process and Costs

Human protection regulation is critical to the drug development process. The accompanying “How-to” document details the regulatory requirements for clinical trial participation. This document discusses the regulatory policy impact on the costs of clinical trial participation, and potential barriers to investigators.

Currently there are multiple sources for regulatory guidelines, the FDA and the Office of Human Resource Protections (OHRP) in HHS as well as the IPH GCP Guidance that has been adopted by the international clinical research community. These agencies have similar roles in subject protections, but their enforcement and levels of investigator compliance monitoring differ, often leading to confusion about which set of regulations prevail for a clinical trial. Recently, there have been attempts to find a common set of rules and regulations for privately and publicly sponsored trials. These legislative approaches and attempts have not yet been successful.

There have also been efforts on the part of federal agencies to reduce the regulatory burdens in research. Some of these burdens may be attributed to the significant changes in the nature and number of clinical trial sites required to conduct translational research focusing on molecular technologies. Given an increase in the number of small investigative sites, regulatory burdens become more pronounced. Cancer Summit workgroup members estimated that between thirty and forty percent of all research funding is used to cover the costs of local regulatory compliance.⁴⁷ A significant portion of those costs for smaller sites are incurred prior to participation in clinical trial activities. The start-up costs associated with regulatory compliance are frequently well above \$5000.⁴⁸

When a low-volume site chooses to participate in clinical trial activities, it does so with the reality that the start-up costs incurred to address prevailing regulatory requirements might not be easily or timely recovered. When the clinical trial activities commence, clinical trials sites have absorbed start-up costs and must then cover ongoing regulatory requirement costs. Regulatory compliance costs, sometimes unpredictable when related to random audits or unplanned requests for information, can be daunting to clinical investigators who are uncertain about the number of accrued participants across whom the regulatory costs might be spread.⁴⁹ NCI’s introduction of the CIRB offers smaller volume investigators the opportunity of timely protocol review, and potentially reduce the need for safety reports and amendment submissions as well as other regulatory costs normally borne locally.

The NIH began its initiative to reduce regulatory burdens in 1999. At that time, it defined “regulatory burden” as any aspect of Federal legislation, regulation, or policy, or Federal/research institution practices that could be made more efficient without diminishing the intended level of protections. At that time workgroups were convened to identify potential streamlining solutions” without diminishing the intended level of protections.”⁵⁰ The NIH acknowledged that the volume of patients accrued to human subject research may influence how difficult it is for local IRBs and smaller community investigator sites to efficiently meet existing regulatory requirements. As a result, NIH convened two separate workgroups based on the size of the research site to address the issues most critical to each.

While multiple initiatives on the part of Federal agencies and the oncology community have been undertaken to reduce regulatory burdens, the cost of regulatory compliance is likely to increase apace the complexity of clinical trials; increasing investigative sites, new agents that require study; and the increasing number of cancer trials. Focusing efforts on reducing overlapping, inefficient and/or burdensome regulations that preserve human subject protection and add to the overall quality of cancer research requires continued focus and commitment on the part of regulators, investigators and all elements of the cancer community.

⁴⁷ Personal communication between Summit Group members and Robert B. Catalano, PharmD, Vice President, Regulatory Affairs, Coalition of Cancer Clinical Groups

⁴⁸ Ibid.

⁴⁹ For example, if you participate as an investigator in one clinical trial over seven years, during this period you could easily be required to have between 35 and 50 interactions with the IRB to be in compliance with regulations. Each of these interactions will require an investigator or staff member to complete the IRB application forms, provide accompanying information with the submission, etc., with each IRB interaction costing your practice at least \$100 or more in staff time for preparation and submission. If in addition you have to review hundreds of safety reports under the current adverse event requirements, your potential costs of minimal participation in one clinical trial protocol begin to escalate astronomically and make participation in clinical trials a financially questionable decision.

⁵⁰ NIH Initiative to Reduce Regulatory Burden. (March 10, 1999). In *National Institutes of Health*. Retrieved August 8, 2006, from <http://grants2.nih.gov/grants/policy/regulatoryburdens/index.htm>.

IV. Barriers to Clinical Trial Participation

There are multiple barriers to increasing clinical participation for physicians and health care providers, and patients. Because clinical trials are not known or well understood by a large number of cancer patients, the receptivity of physicians to clinical trials and their willingness to encourage trial participation is important to encourage greater patient participation in clinical trials.

A. Workforce Issues

There has been a wide range of opinion regarding the supply and demand for physician services over the past five years. There is an emerging consensus that a nationwide physician shortage in certain specialties will manifest over the next decade. According to The Lewin Group's most recent work for the National Center for Health Workforce Analysis, growth in demand will be the highest among physician specialties that predominantly serve aging populations. Based on current trends, demand for internal medicine sub-specialists (this classification includes hematology and hematology/oncology) between the years 2005 and 2020 is projected to grow 27 percent to approximately 90,200 while supply for the same period is projected to grow by 12 percent to approximately 78,500.⁵¹

The American Association of Medical Colleges (AAMC) also indicates that "mounting analytical work, as well as anecdotal evidence, suggests that current trends will culminate in a shortage of physicians within the next few decades." The AAMC has called on medical schools nationally to increase their undergraduate class sizes by 30%.⁵² The AMA has responded by adopting the policy position that "there is a shortage of physicians, at least in some regions and specialties, and that evidence exists for additional shortages in the future."⁵³ Since cancer is primarily a disease of older people, longevity is likely to contribute significantly to an increasing demand for cancer care services.

The AAMC and the ASCO are conducting a comprehensive study to assess the future supply of clinical oncologists to more specifically address questions of the oncology workforce, preliminary results of which are to be released in the next several months.⁵⁴ They noted:

Once primarily an acute-care specialty, cancer treatment is undergoing a fundamental shift that focuses heavily on chronic-care management, as well. The transition has become more noticeable as more patients have survived longer after being treated for cancer, and as more people have reached the cancer prone years of 65 and beyond. From 1998 to 2002, according to the National Cancer Institute, the median age at which cancer was diagnosed was 67, with more than 26 percent of people between the ages of 65 and 74 being diagnosed. In contrast, among people aged 35 to 44, only about 6 percent were diagnosed with cancer.⁵⁵

Participation in accredited hematology and oncology residency programs has not increased.⁵⁶ The number of available residency slots has decreased despite the increase in demand for such services over the past several years. The growing aging population will contribute a 22 percent increase in demand for physician services between 2005 and 2020.⁵⁷ The projected shortfall of sub-specialists could impede goals of increasing participation in clinical

trials, particularly when combined with other barriers to physician participation described below.

There are additional concerns on the part of the American Association for Cancer Research regarding an increase in trial funding in other nations across the globe, regarding the loss of investigators who choose to conduct research in other countries and the subsequent "eroding" of the United States competitive advantage in cancer agent development.⁵⁸

B. Investigator and Patient Participation in Trials

In addition to the anticipated physician shortages and decreasing numbers of physicians available to participate in clinical trials, there are a number of other challenges associated with increasing physician and patient participation in clinical trials. For physicians, these challenges include increasing budget and time constraints associated with related to decreases in clinical reimbursement and the reduced ability to make in-kind contributions to research efforts from their practices. There are administrative burdens related to clinical trials that make many hesitant to participate given additional costs and expenses specific to clinical trials that may be inadequately reimbursed. In addition, some physicians fear they will "lose control" of their patients' care if they participate, while others are unaware of clinical trials.⁵⁹ Access to clinical trials also appears to be a barrier for physician participation. A survey conducted by the Oncology World Congress estimated that less than half of oncologists "are satisfied with their access to clinical trials."⁶⁰

In 2003, NCI published a document reflecting plans and priorities for cancer research, treatment and prevention trials. In this document, the NCI observes that physician barriers to clinical trial participation are tangible. The NCI observes:

"in particular the reimbursement that NCI provides physicians for their role in clinical trials often falls far short of their costs and is well below what the pharmaceutical industry provides. Physicians who take part in clinical trials often must hire additional nursing and data management staff to ensure that patients fully understand the risks and benefits of participation, track participating patients, and collect and report the necessary data."⁶¹

There is also concern in the oncology community that the level of diversity in accrued participants is not sufficiently representative of both minority populations and older patient populations.⁶²

One of the major barriers to cancer clinical trials is the lack of awareness about the possibility of participation. A recent survey conducted by the Coalition of Cancer Cooperative Groups showed that only 10 % of cancer survivors were aware that participation in a clinical trial might be a possibility in or around the time of their diagnosis. The primary source of clinical trials awareness is the physician; in 74% of the survivors. Thus the dialogue between the physician and patient is critical to the entire process. Addressing the physician related disincentives to participation is therefore essential if continued progress is to be made. Although not all cancer patients are eligible for a given clinical trial, clinical trials are now available for most stages of the major cancers. In 2003, Comis et al. estimated that approximately 200,000 newly diagnosed patients would be eligible and willing to participate in NCI-type trials, yet only 20-25,000 patients participate in such studies.⁶³ The continued slow rate of accrual will continue to produce serious lag times in bringing new, effective cancer therapies to the public.

As fewer physicians participate in clinical trials due to other pressures in their clinical practice environment, patient recruitment to clinical trials becomes increasingly challenging. It should be noted that approximately 75 percent of the patients surveyed said they would have been willing to enroll had they known it was possible.⁶⁴

⁵¹ The Lewin Group. The Physical Workforce: Projections and Research into Current Issues Affecting Supply and Demand, Final Report Prepared for National Center for Health Workforce Analysis, Bureau of Health Professionals. June 30, 2006.

⁵² American Academy of Medical Colleges. AAMC Statement on the Physician Workforce. June 2006.

⁵³ American Medical Association. Report of the Council on Medical Education – Subject: The Physician Workforce: Recommendations for Policy Implementation (Resolution 312, A-04; Resolution 319, A-04, Resolve 1). CME Report 8-A-05.

⁵⁴ Two National Medical Groups Will Assess the Supply and Demand of Clinical Oncologists for the Next 20 Years. In AAMC. Retrieved June 26, 2006, from <http://www.aamc.org/newsroom/pressrel/2005/050420.htm>.

⁵⁵ AAMC Reporter: As Cancer Patients Live Longer, Providers Shift Focus. (January 2006). In AAMC. Retrieved June 26, 2006, from <http://www.aamc.org/newsroom/reporter/jan06/cancer.htm>.

⁵⁶ American Council on Graduate Medical Education. Number of Accredited Programs by Academic Year. In *Accreditation Council for Graduate Medical Education*. Retrieved June 30, 1996, http://www.acgme.org/adspublic/reports/accredited_programs.asp.

⁵⁷ The Lewin Group. The Physician Workforce: Projections and Research into Current Issues Affecting Supply and Demand, Final Report Prepared for National Center for Health Workforce Analysis, Bureau of Health Professionals. June 30, 2006.

⁵⁸ Funding for, and Societal Impact of, Cancer Research to Be Discussed. American Association for Cancer Research. March 28, 2006.

⁵⁹ McCaskill-Stevens, W et al. Increasing Minority Participation in Cancer Clinical Trials: The Minority-Based Community Clinical Oncology Program Experience. *Journal of Clinical Oncology*. August 1, 2005; 23 (22): 5247-5254.

⁶⁰ Inaugural Oncology World Congress Opened with a Focus on Practice Topics, Reimbursement, and Clinical Trials. First Annual Oncology Congress. (November 16, 2005). In *Oncology Congress*. Retrieved July 5, 2006, from <http://www.oncologycongress.com>.

⁶¹ Plans and Priorities for Cancer Research. (2003). In *National Cancer Institute*. Retrieved July 6, 2006, from <http://plan2003.cancer.gov>.

⁶² Townsley, C et al. Systematic Review of Barriers to the Recruitment of Older Patients With Cancer Onto Clinical Trials. *Journal of Clinical Oncology*. May 1, 2005; 23(13): 312-324.

⁶³ Comis, RL et al. Public Attitudes Toward Participation in Cancer Clinical Trials. *Journal of Clinical Oncology*. March 2003; 21 (5): 830-835.

⁶⁴ Coalition of Cancer Cooperative Groups. Most Cancer Patients Satisfied with Clinical Trial Experience, Yet, Few Aware of Opportunity: Study Shows Improved Physician-patient Communications Could Increase Enrollment in Cancer Clinical Trials. (June 5, 2006). In *Coalition of Cancer Cooperative Groups*. Retrieved August 10, 2006, from <http://www.cancertrials-help.org/shared/pressTemplate.jsp?ID=2120&VID=10009>.

In addition, the “Eliminating Clinical Disparities in Clinical Trials [EDICT] Project” managed by the Chronic Disease and Control Research Center at Baylor College and the Intercultural Cancer Council, stresses the importance of adequate women and minority representation in clinical trials and in an Executive Summary states, “National Institutes of Health Revitalization Act of 1993 [Public Law 103-43] established guidelines for the inclusion of women and minorities in government sponsored human subject clinical research.” EDICT believes that “[w]ithout adequate minority representation, researchers can neither assess differential effects among groups nor ensure generalizability of clinical trials. Barriers to clinical trial participation by minority and underserved populations include the simple lack of information and culturally appropriate materials, socioeconomic and cultural factors, as well as a mistrust of the medical research establishment.”⁶⁵

This suggests that government agencies may need to direct more attention to monitoring compliance with this mandate as well as provide adequate resources to the research community to facilitate compliance.

C. Financial Constraints

Financial constraints include reimbursement levels that have not universally kept pace with increasing practice operating costs and frequently result in competing financial priorities that interfere with the ability to support clinical trials operations integrated into a clinical practice setting. Furthering financial pressures, the Medicare Modernization Act (MMA) of 2003 introduced cuts to drug reimbursement rates and a reduction in administration fees⁶⁶, possibly forcing some oncologists to reconsider their participation in trials.

Public financial support is also waning. The Federal budget for cancer research has decreased over the past two fiscal years. The 2006 budget provided \$31 million less for cancer research than in 2005, and the proposed 2007 budget shows an additional \$40 million reduction in cancer research.

Publicly funded clinical trials have been consistently under-funded and continue to be available because physicians and institutions volunteer individual time and resources and identify ways to cross-subsidize these efforts.⁶⁷ The unfunded costs of conducting publicly funded clinical trials are additive to physician practice and institutional expenses and are dependent on in-kind contributions of non-compensated staff time and other progressively less available practice resources.

There are significant costs associated with clinical trials including: protocol development, data collection and management, research physician and nursing time, analysis of results, clinical laboratory tests and x-rays and the cost of the agent(s) or treatment(s) being tested. Many of these costs are borne by the sponsoring organization, either a public entity or a pharmaceutical company. There are often costs in excess of available reimbursement, particularly in publicly funded clinical trials.

In the 2004 Lewin study on clinical trial costs, labor accounted for more than seventy percent of total clinical trial costs. The non-labor portion of total research costs typically increased if the research enterprise was affiliated with an academic medical center. Sites not affiliated with an academic medical center typically used more than ninety percent of clinical trial revenues to support staff salaries and other staff-related costs including benefits.⁶⁸

C-Change reported that the cost of cancer clinical trials even at the larger and generally more efficient clinical trial research sites varies significantly depending on the nature of the trial and whether it was publicly or privately sponsored. The Lewin study, based on 2004 data, found that publicly sponsored studies are generally under-funded. Those research centers participating in the C-Change study reported that they relied on non-trial sources of revenue to cover costs such as salaries and overhead, and reported on average that 25 percent of their revenue for both

public and private trials subsidized originated from non-trial sources. An important part of managing clinical trial selection for these sites in order to minimize losses appears to be ensuring a mix of privately and publicly sponsored trials, where the industry sponsored trials cross-subsidize the publicly sponsored trials.

D. Technology Induced Cost Barriers

The recent approval of targeted and vaccine therapies, and other patient specific treatments, will require more sophisticated infrastructure in sites participating in clinical trials, in order to effectively collect, process, store and ship study samples. These are also additive costs that will affect the overall cost of clinical trials such as sophisticated patient safety monitoring and outcomes measurement systems. The current allocation of public monies for cancer clinical trials may not support the changing paradigm of cancer research where new technologies are paving the road for personalized medicine.

The technological landscape of cancer research is rapidly widening the breadth of understanding of and treatments for cancer patient and the current decrease in public funding for clinical trials may not adequately support the increasingly complex infrastructures associated with new cancer research. Much of this advanced infrastructure, focused on the development of cancer biomarkers and genomic medicine, is not likely to be funded by industry.

V. Clinical Trial Outlook

The future of clinical trials is uncertain and portends the erosion of investigator and institutional commitment to cancer clinical trials as the current health care system faces growing financial constraints and a potential shortage of oncologists and trained cancer researchers. Even those physicians and research centers who currently participate in clinical trials and have employed the best practices as identified in the companion document on methods for clinical trials are encountering increasing restraints in their ability to continue working on the same number of publicly funded trials.⁶⁹

This ongoing erosion of institutions’ and physicians’ willingness to participate in trials which often cover less than seventy percent of an institution’s costs of performing trials will become a greater issue as workforce shortages arise, patient demographics increase demand for cancer services, and new targeted cancer research requires more complex and expensive infrastructure. One survey indicated that two thirds of practicing oncologists reported the lack of needed infrastructure to conduct trials, highlighting the importance of education not only on the regulatory aspects of conducting clinical trials but in providing infrastructure support.⁷⁰

The issues raised in this report must be examined more closely and addressed with a variety of public policies and financial support in order to increase the awareness and participation in clinical trials needed to speed the movement of new drugs and treatments into standard cancer care.

⁶⁵ Background. In *Baylor College of Medicine*. Retrieved August 30, 2006, from <http://chronic.bcm.tmc.edu/edict/background.html>.

⁶⁶ New Bulletin. In *Association of Community Cancer Centers*. Retrieved on July 25, 2006 from http://www.accc-cancer.org/stasoc/NA/newsletters/VAnews_summer06.htm.

⁶⁷ This has typically been done by either increasing other profitable services offered and/or by conducting industry-sponsored trials at the same sites which more generously reward industry-directed research activity.

⁶⁸ The Lewin Group. *A Guidance Document for Implementing Effective Cancer Clinical Trials*, Version 1.2. June 7, 2005.

⁶⁹ The key success factors in best practices, as outlined in “A Guidance Document for Implementing Effective Cancer Clinical Trials, Version 1.2 published by The Lewin Group in June 2005, included having a committed staff, adequate financial resources, access to ancillary services, showing respect for subjects, having a supportive sponsoring institution, and placing emphasis on patient care.

⁷⁰ Somkin, C et al. Organizational Barriers to Physician Participation in Cancer Clinical Trials. *Am J Manag Care*. 2005; 11:413-421.



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