



A Guidance Document for Implementing Effective Cancer Clinical Trials

Executive Summary

Version 1.2

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PREFACE

Cancer clinical trials represent a structured, scientific approach to advancing knowledge in the pursuit of new diagnostic, treatment, monitoring, and prevention modalities. In 2005, the American Cancer Society projected 1,372,910 new diagnoses of, and 570,280 deaths from cancer. Cancer is currently ranked second, only to heart disease, among the most common causes of mortality in the United States, accounting for almost a quarter of US deaths.¹ Still, fewer than 5 percent of adult cancer patients enroll in clinical trials.²

The complexity, expense, and length of major clinical trials limit the number of trials undertaken. To investigators and research institutions, regulatory requirements for clinical trials are confusing, often broadly interpreted, and perhaps inconsistently implemented. The cancer clinical trial arena is beset with inconsistent cost accounting and research revenue distribution methods. Patients, investigators, institutions, and providers might perceive greater health and cost risk in their involvement in clinical trials, in part, because of this confusion. It is difficult to know the risks involved if the rules are not well-known and understood.

Data on the cost of conducting clinical trials are limited. The general perception among researchers is that reimbursement for cancer clinical trials does not sufficiently cover costs; however, few investigative sites collect data to confirm this perception. These reimbursement hurdles reduce the attractiveness of clinical trials for potential investigators.³

C-Change commissioned The Lewin Group and Lovett Collins Associates, LLC (Lovett Collins), to create an industry guidance document for conducting Phase II and Phase III cancer clinical trials. C-Change, The Lewin Group, and Lovett Collins worked closely with the Summit on Cancer Clinical Trials to develop this document.

This document provides public- and private-sector policymakers, cancer researchers, institutions, and trial funding sources with information regarding regulatory requirements and guidance on the functional requirements and costs associated with conducting Phase II and III cancer clinical trials. This document identifies operational and cost benchmarks for sites currently conducting cancer clinical trials, offers sites interested in or recently new to clinical trials guidance from experienced clinical trial organizations, and examines how the costs associated with conducting clinical trials compare to reimbursement levels for trial participation.

¹ "Cancer Facts & Figures 2005." The American Cancer Society. "Cancer Statistics 2005." The American Cancer Society.

² Comis RL, Aldige CR, et al. "A Quantitative Survey of Public Attitudes Towards Cancer Clinical Trials." The Coalition of National Cancer Cooperative Groups, The Cancer Research Foundation of America, Cancer Leadership Council, and Cancer Oncology Nursing Society, 2000.

³ Comis, et al., op. cit.

Acknowledgments

Several individuals contributed to this project. The Lewin Group and Lovett Collins worked with a Technical Advisory Panel (TAP) to complete this document. The TAP nominated sites to survey and provided input regarding the structure and content of the survey instrument. The survey served as the primary source of information for this guidance document.

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EXECUTIVE SUMMARY

This document identifies operational and cost benchmarks for sites currently conducting cancer clinical trials. For sites interested in, or new to, clinical trials, the document offers guidance and examines, among other metrics, how the costs associated with conducting clinical trials compare to reimbursement levels. This document represents a first iteration of a guidance document for structuring effective cancer clinical trials. It provides information pertinent to providers, payers, and policymakers to structure, perform, and fund compliant and effective cancer clinical trials.

Information in this document was primarily gathered from a survey administered to a sample of 14 clinical trial sites. Respondents included sites affiliated with hospitals, independent practices, and sites participating in the NCI-funded community clinical oncology programs (CCOPs). Survey data were supplemented with information obtained from a review of the literature on cancer clinical trials and a review of regulations governing the conduct of cancer clinical trials. Randomized Phase II and Phase III mock protocols were used to achieve a comparative benchmark for time and labor cost requirements. The same protocols were used with variations in assumptions based on the study sponsor, government or industry. The time and labor cost results reported in the tables relate to the mock protocols. Additional details regarding the survey, respondents, and data methods are found in *Appendix B, Methodology*.

It should be noted that the Phase II trial is a randomized Phase II study employing intravenously administered combination chemotherapy with a random assignment to open label treatment with an intravenous monoclonal antibody. This type of trial is much more complex than a simple Phase II study, and such designs are becoming more prevalent as newer biologics are being evaluated. The Phase III trial is a double blind, randomized, placebo controlled evaluation of an agent which is given by an initial intramuscular loading dose followed by an oral formulation. In certain ways, this study is less labor intensive than the randomized Phase II study.

The survey defined nine functional steps, which include: 1) Securing the Protocol, 2) Internal Study Feasibility Decision Process, 3) IRB Submission, 4) Legal/Financial Review and Contract, 5) Site Approval, 6) Preparation for Study Execution, 7) Study Execution/Procedures, 8) Data Review, and 9) Study Closeout. Detailed time and labor cost results are reported by functional area to better understand where the labor costs are found.

The “Cancer Clinical Trials: Elements of Success (EOS),” developed by the Summit Series on Cancer Clinical Trials, was reviewed in the context of survey responses and in the analysis of the data. The EOS include: 1) Committed Staff, 2) Adequate Financial Resources, 3) Accessible Ancillary Services, 4) Respect for Subjects, 5) Sponsoring Institution, and 6) Emphasis on Safe Patient Care. We found an overall consistency between survey responses and the EOS. Themes from the EOS carried throughout each of the functional areas necessary for the successful completion of cancer clinical trials and are seen within the best practices reported by respondents.

We identify the key findings of the survey below, beginning with total study costs and concluding with findings regarding processes and best practices.

- We found the median study cost per subject based on the mock protocols for the government-sponsored randomized Phase II study was \$6,266, whereas the cost for the industry-sponsored randomized Phase II study was \$8,450. The median cost per subject for the government-sponsored Phase III study was \$3,427, whereas the cost for the industry-sponsored Phase III study was \$4,696. Industry trials were found to be more research intensive than government trials, which is consistent with the literature.
- Government-sponsored studies are generally under-funded. Government-sponsored studies reimburse at approximately \$2,000 per study subject (*Exhibit ES-1*). The randomized Phase II government-sponsored study median cost was \$6,266, whereas the Phase III median cost was \$3,427. The reported 25th percentiles were \$3,618 and \$1,966, respectively. This means that the total cost of the mock studies for more than three-quarters of sites would not be covered. The reimbursement for an industry-sponsored study is variable, based on clinical trial agreement. (*For detailed information see page 46.*)

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

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

- Effective trial selection requires a mix of government- and industry-sponsored trials to help minimize losses associated with conducting government-sponsored trials. Respondents relied on non-trial sources of revenue to cover costs such as salary and overhead. Non-trial sources include grants, third-party payer sources, and clinical practice revenue. (*For detailed information, see page 54.*)
- Respondents reported that, on average, 29% of their revenue originated from non-trial sources. This suggests that a strong institutional commitment is needed for sites to participate in cancer clinical trials. (*For detailed information, see page 54.*)
- Median non-labor cost as a percent of total study costs was 28% among respondents. The non-labor cost was higher for research enterprises affiliated with academic medical centers compared to research enterprises not affiliated with to academic medical centers. (*For detailed information, see page 55.*)

- As demonstrated in *Exhibit ES-2*, respondents for the government-sponsored study would have covered labor cost for less than half of the responding sites. The reimbursement provided by industry-sponsored studies is variable and its ability to cover labor costs depends on the exact negotiated reimbursement level. (For detailed information see pages 32, 33, 40, and 41.)

Exhibit ES-2: Reported Labor Cost per Subject for Sample Randomized Phase II and III Studies (non-labor costs excluded)

Reported Labor Cost per Subject					
		Per Subject Reimbursement	Median	25th Percentile	75th Percentile
Randomized Phase II	Government-Sponsored	\$2,000	\$4,903	\$2,906	\$7,274
	Industry-Sponsored	Variable	\$6,741	\$3,650	\$8,438
Phase III	Government-Sponsored	\$2,000	\$3,006	\$1,563	\$5,499
	Industry-Sponsored	Variable	\$3,651	\$1,949	\$7,756

- Sites should consider carefully staff time and effort and the potential for accrual to studies before accepting a clinical trial. High accrual in fewer studies appears more favorable than low accrual in more studies because of fixed cost to start trials. Among open industry trials, a median of 63% had subjects enrolled, compared to a median of 56% of government trials with subjects enrolled. The percent of open trials with subjects enrolled is important because many of the costs associated with clinical trials are incurred during the study’s start-up phase and are fixed and independent of the number of subjects enrolled. These costs are not separately covered by government-sponsored studies. *Exhibit ES-3* demonstrates the pre-subject enrollment costs. These costs are incurred independent of study accrual rates. (For detailed information, see pages 32, 33, 40, 41, and 50.)

Exhibit ES-3: Reported Total Study Pre-Subject Enrollment Costs for Sample Phase II and III Studies

Reported Total Study Pre-Subject Enrollment Cost				
		Median	25th Percentile	75th Percentile
Phase II	Government-Sponsored	\$5,645	\$2,273	\$15,290
	Industry-Sponsored	\$8,613	\$5,976	\$15,885
Phase III	Government-Sponsored	\$5,361	\$2,866	\$16,669
	Industry-Sponsored	\$8,627	\$5,927	\$15,961

- Successful subject recruiting is integral to reaching long-term clinical trial success to recover pre-subject enrollment costs. Without the full support of the principal investigator (PI), studies often fail to meet accrual targets. To be effective, PIs must fully leverage their

research staff to improve trial execution and the opportunities for success. *(For detailed information, see page 24.)*

- Survey sites noted two complementary financial elements critical to success: (1) adequate compensation for clinical trials; and (2) the need to control expenses and perform efficiently. Surveyed sites indicated the importance of selecting trials appropriate to their patient population. Trial selection drives costs and compensation. Trials should be evaluated based on their pertinence to patient populations and the ability to reasonably accrue subjects. *(For detailed information, see pages 46 and 50.)*
- Effective ancillary processes are necessary for clinical trial success. Sites should have ready access to all ancillary services that are regularly needed so that patients are not discouraged from participating in trials by the need to travel to other locations (EOS 3). *(For detailed information, see page 8.)*
- Labor cost appears to be the greatest contributor of cost to conducting cancer clinical studies. Reported median sample study hours ranged from approximately 67 hours per subject to more than 127 hours per subject as demonstrated in *Exhibit ES-4*. Industry-sponsored studies for both the randomized Phase II and the Phase III trials take more time and effort than government-sponsored studies due to contracting issues, inconsistent regulatory requirements and forms, and a higher degree of complexity with less clarity in data collection. *(For detailed information, see pages 32, 33, 40, and 41.)*

Exhibit ES-4: Reported Study Time per Subject for Sample Randomized Phase II and III Studies (in hours)

Reported Study Time per Subject (in hours)				
		Median	25 th Percentile	75 th Percentile
Randomized Phase II	Government-sponsored	81.9	59.3	130.7
	Industry-sponsored	127.5	96.6	179.1
Phase III	Government-sponsored	67.1	35.5	92.5
	Industry-sponsored	86.4	49.1	132.1

- More than 70% of revenues from conducting cancer clinical trials are allocated to staff salary. Sites without academic affiliation dedicated a median of more than 90% of research revenue to salary. This differential could be attributed to higher non-labor costs typical of academic medical centers. *(For detailed information, see page 55.)*
- As demonstrated in *Exhibit ES-5*, average labor cost per hour ranged from approximately \$41 to just over \$62, depending on trial phase and study-sponsor. This \$20 differential is the primary source of variation in cost. The implication of this is that sites vary in how they use their staff to complete cancer clinical trials. Opportunities exist to reduce cost by allocating the right mix of staff to the right tasks. *(For detailed information, see page 46.)*

Exhibit ES-5: Reported Average Labor Cost per Hour across Study Phase and Sponsor

Reported Average Labor Cost per Hour				
Study Type		Median	25th Percentile	75th Percentile
Phase II	Government-sponsored	\$55	\$41	\$61
	Industry-sponsored	\$47	\$45	\$55
Phase III	Government-sponsored	\$55	\$43	\$63
	Industry-sponsored	\$48	\$41	\$53

- Regulations govern most functional steps required for conducting clinical trials. Of the nine functional steps identified, six include elements relate to federal regulations: 3) Institutional Review Board (IRB) Submission; 5) Site Approval; 6) Preparation for Study Execution; 7) Study Execution; 8) Data Review; and 9) Study Closeout. These six functional steps include IRB approval, SAE reporting, source documentation, training requirements, monitoring visits, document storage, and investigator approval paperwork. *(For detailed information, see pages 16-29.)*

Consistent with the literature review and based on data collected from respondents, the barriers to enter the cancer clinical trial industry for new researchers are high. Such barriers include: lack of consistency across practices for processes, need for research structure, and regulations. In addition, there is little awareness of costs associated with cancer clinical trials. This document attempts to provide clarity and understanding regarding the cost drivers, functional requirements, and processes involved with implementing cancer clinical trials. Understanding these factors is important for developing effective cancer clinical trial programs. This document serves as a first step in a continuing effort to document costs and best practices of conducting cancer clinical trials.