Attributes of Exemplary Research

Clinical Research Site Infrastructure and Efficiency

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Efficiency is imperative in the process of designing and implementing clinical trials. This journal article, part of the series on attributes of exemplary research sites, focuses on infrastructure improvements that promote efficiency. This article begins with a brief overview of current health systems research findings, reviews current initiatives undertaken by the National Cancer Institute (NCI), and presents examples of helpful practices implemented at some research sites. The authors have included content that will be helpful to all sites that conduct clinical trials, including community-based and academy-affiliated centers.

Increasing efficiency in the clinical trials development process will help ensure a vibrant clinical trials system that makes best use of limited resources and keeps pace with rapidly advancing scientific discoveries in the field of cancer research.

Current Research

Increased efficiency is crucial in all phases of clinical trial development and implementation. Recent research presented at the 2010 ASCO Annual Meeting underscores this imperative. In one abstract, Dilts et al¹ presented outcomes from their evaluation of the Marker Validation for Erlotinib in Lung Cancer (MARVEL) trial, which was a phase III biomarker trial sponsored by the National Cancer Institute (NCI) that closed early because of poor accrual. As the abstract authors found, the trial development process took 2.5 years, ultimately resulting in reduced enthusiasm about the trial and decreased scientific relevance because of a standard-of-care changes that occurred while the trial was being developed. The trial had an initial recruitment goal of 1,200 patients and received institutional review board (IRB) approval at more than 300 sites; however, poor accrual led to early trial closure, with only 23 patients having been randomized. The authors concluded that “with the rapid development of scientific knowledge, clinical trial development times should be shortened to maintain the validity and relevance of the questions addressed.”¹

In another abstract presented at the 2010 ASCO Annual Meeting, Cheng et al² found that trials that did not have a patient enrolled within the first 2 months of trial activation were significantly less likely to achieve their minimum accrual target, despite the length of time the trial remained open. The authors also found that only 18.5% of clinical trials sponsored

by the NCI Cancer Therapy Evaluation Program achieved their minimum accrual goal within the anticipated period.²

Evaluating this topic from a different angle, Durivage et al³ presented an abstract at the 2009 ASCO Annual Meeting that examined accrual to Cooperative Group-Industry-sponsored trials at 14 NCI-designated comprehensive cancer centers. The authors found that 54.2% of the 2,685 therapeutic clinical trials open at these centers did not accrue any patients.³ On the basis of these findings, authors estimated that each of the evaluated cancer centers dedicate roughly 3,773 hours annually to trials that accrued no patients, at an annual cost of \$81,000 per center. The authors also determined that only 26.6% of the Cooperative Group-Industry-sponsored trials accrued more than two patients, and these trials accounted for nearly 90% of the sites' overall accrual to Cooperative Group-Industry trials.³ Recognizing that relatively few trials account for the majority of participant accrual, the authors called for development of effective strategies to guide trial selection and rules for prompt closure of nonaccruing studies to better direct resources to trials with the greatest promise of patient enrollment.

A subsequent abstract present by Durivage et al⁴ at the 2010 ASCO Annual Meeting examined the performance of 170 phase II investigator-initiated trials at nine cancer centers. The authors found that 47% of the trials closed before completion and that 21% (684) of patients who enrolled onto these trials participated in a trial that closed as a result of poor accrual.⁴ The authors found that slow-accruing trials remained open for a median of 28 months and that significant resources were exhausted on trials that were not completed.⁴ The data presented in this abstract highlight the importance of research sites implementing operational changes in regard to investigator-initiated trials, not only trials offered through the Cooperative Group system.

The abstracts presented here provide a brief overview of current health systems research related to clinical trials efficiency. Although challenges within the system undoubtedly exist, efforts at both the national and site levels offer promise for revitalizing the cancer clinical trials system and continuing to meet the needs of the rapidly advancing field of cancer research. By making infrastructure improvements that promote efficiency, sites will be able to better serve patients by more rapidly translating basic scientific discoveries into clinical care.

Table 1. Operational Efficiency Working Group–Suggested Initiatives for Reducing Trial Activation Times

Initiative	Goals and Actions
A	Reduce the time to activation of Cooperative Group phase III trials
A1	Each Cooperative Group will develop an action plan to achieve the agreed-on OEWG target timeline for trial activation.
A2	CTEP will develop an action plan to achieve the agreed-on OEWG target timeline for trial activation.
A3	CTEP and the Cooperative Groups will develop collaborative processes for revision of concepts and protocols that meet the agreed-on OEWG timeline.
A4	NCI and the Cooperative Groups will collaborate in developing approaches to reward performance against timelines.
B	Reduce the time to activation of CTEP phase II early drug development trials
B1	CTEP will develop an action plan to achieve the agreed-on OEWG target timeline for trial activation.
B2	CTEP will collaborate with phase II early drug development trial performance sites to develop processes for revision of letters of intent and protocols that meet the agreed-on OEWG timelines.
C	Reduce time to activation of NCI-designated cancer center investigator-initiated trials
C1	Each cancer center will develop an action plan to achieve the agreed-on OEWG target timeline for trial activation.
C2	NCI and cancer centers will develop and implement new initiatives designed to streamline university contracting and financial review processes.
D	Reduce time to activation of all categories of trials
D1	NCI, Cooperative Groups, and cancer centers will develop a coordinated approach to standardization of protocol elements and protocol development tools.
D2	NCI will enhance funding and capabilities for use of biomarkers in clinical trials.
D3	Cancer centers will perform a rigorous review of each proposed clinical trial concept in advance of protocol development.
E	Improvements to enhance NCI's clinical trials program (not directly related to reducing activation times)
E1	NCI and academic institutions will provide incentives to enhance cancer center participation in Cooperative Group and other multisite clinical trials.
E2	Cancer centers will develop a process for the periodic strategic review of their clinical trial programs.
E3	NCI will develop enhanced clinical research mentorship and training programs at cancer centers.

NOTE. Data adapted.⁶

Abbreviations: OEWG, Operational Efficiency Working Group; CTEP, Cancer Therapy Evaluation Program; NCI, National Cancer Institute.

Operational Efficiency at NCI

The NCI has taken a proactive stance regarding the growing library of literature related to clinical trial efficiency. In December 2008, the NCI Clinical Trials and Translational Research Advisory Committee established the Operational Efficiency Working Group (OEWG) to advise NCI on strategies to reduce protocol activation times of NCI-sponsored trials. Composed of experts in the field of cancer clinical research, OEWG compiled a report that proposed the establishment of enforceable deadlines for protocol development and implementation. Failure to meet these timelines will result in protocol termination. The report also proposed 14 broad initiatives to improve efficiency and increase the feasibility of protocol activation within the established timelines.⁶ The OEWG report was approved in March 2010.

The report includes protocol activation targets of 300 days for phase III trials, 210 days for phase II trials, and 90 days for investigator-initiated trials at NCI-funded cancer centers.⁶ Protocols that have been in the review process for 24 months (for phase III trials) or 18 months (for phase 2 trials) will be terminated. Termination will occur regardless of any activation issues outside the control of the Cooperative Groups or Cancer Therapy Evaluation Program, such as delays caused by contracting with industry partners or IRB review. The 24- and 18-month deadlines will apply retroactively to trials already in the system, beginning in January 2011.⁶

OEWG made several suggestions for mechanisms that will be put in place to assist practices, such as supplemental funding

grants to support staffing changes, development of action plans, and educational opportunities. Table 1 outlines the 14 proposed initiatives, and the full OEWG report is freely accessible to the public online.⁶

Best Practices

As the NCI Cooperative Groups work to promote clinical trial efficiency, sites that conduct NCI-sponsored trials are also improving their internal infrastructures. Efficiency at the site level

ASCO Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites

The ASCO statement addresses the minimum requirements for sites conducting quality clinical trials as well as the attributes of exemplary sites. Both minimum requirements and exemplary attributes were based on a review of the literature, current regulatory requirements, and consensus among community and academic clinical researchers. In order to conduct quality clinical research, sites should meet the minimum requirements. It should be noted, however, that the exemplary attributes are voluntary and are suggested as goals, not requirements. Not all attributes will apply to all clinical trial sites, and many sites may be able to conduct high-quality clinical trials without acquiring all attributes.

will help ensure that scientifically relevant trials are not dismissed because NCI timelines were not met. Beyond protocol development, infrastructure changes will also help sites make best use of resources and accrue to their greatest potential.

Many sites have developed specific committees focused on evaluating the feasibility of new protocols and proposed concepts at the site level. Before proposed clinical trials undergo scientific review, the Feasibility Committee reviews the initial protocol to determine whether it should be implemented at the site. The feasibility review focuses on the likelihood that the trial will be successful at the site, including evaluation of site-specific factors such as adequate targeted patient population, overlap with related trials, and the site's ability to meet imaging- and specimen-processing requirements. In the case of investigator-initiated trials, both the Scientific Review Committee and Feasibility Committee should review a new concept before time is spent drafting a protocol. This review is not only a good practice, but is also a recommendation of the OEWG.

When developing investigator-initiated protocols, many sites have benefited greatly from the use of scientific writers to assist with drafting new protocols. The expertise of experienced protocol writers can help principal investigators write solid protocols that best meet the requirements of the research site and trial sponsor. Ideally, this streamlined process leads to fewer protocol revisions and quicker trial implementation. For example, the scientific writer can ensure that important but potentially overlooked components of the protocol are addressed, such as inclusion of a recruitment plan, realistic eligibility criteria, and cost-efficient testing and procedures. In addition, scientific writers can help improve internal consistency across therapeutic areas at the site by working with principal investigators to ensure that consistent language is used and that any site-specific needs are addressed. It should be acknowledged that the use of scientific writers is not feasible at all research sites. However, many sites have been able to overcome this hurdle by applying for supplemental administrative grants to offset the costs.

Sites have also improved efficiency by establishing internal deadlines for various aspects of the clinical trial development process. By working with investigators, IRBs, and other research staff, sites can establish timelines for various aspects of protocol development and implementation. For example, one site established a rule that all investigators must respond to IRB inquiries within 72 hours. This simple rule resulted in a reduction of the number of days it took the IRB to review and approve submissions at the site. Many sites have also established parallel review processes. Tasks such as contracting and budgeting are often conducted simultaneously, thus reducing the time to trial activation. Establishing a culture in which all members of the research team understand the importance of conducting their role in an efficient manner is imperative. For example, instead of waiting several days for an e-mail correspondence regarding the trial contract, staff members know that to meet site-established deadlines, they need to be proactive and contact the other party by phone if response time is insufficient.

Timelines are also established to evaluate each trial's accrual rate at specific intervals. Some sites evaluate trial accrual every 6

months and require the principal investigators of nonaccruing trials to develop an action plan indicating how recruitment will be facilitated. If accrual does not improve on that specific trial, many sites have established rules to close any nonaccruing trials. The effectiveness of such policies depends on consistent implementation and enforcement. In some situations, sites have found more competitive ways to promote accrual, such as by compiling a monthly accrual report that compares investigators recruitment statistics each month. Investigators can see where their accrual stands in comparison to their peers, which often promotes increased accrual efforts. This type of exercise also provides principal investigators with frequent data about their trials so corrective action can be taken long before a trial is at risk of being closed by the site due to inadequate accrual.

Computerized tracking systems are used by many sites to assist with efficiency. These systems help keep track of timelines and facilitate organization at the site. In some cases, computerized systems can even be used to submit documents to the IRB. The capabilities of the systems vary by sites and depend on their specific needs. Sites may choose to purchase a standardized system or have a system built specifically for their needs.

Strategic review of operations at the clinical research site is also a critical aspect of improving a sites' infrastructure and is included as an OEWG recommendation. One aspect of this review should include evaluating the site's portfolio for balance among Cooperative Group, investigator-initiated, and industry-sponsored trials. Scientific relevance is also important, and sites should offer trials that are engaging to investigators and have the potential to result in practice-changing clinical advancements. Trials offered at the site must also have an adequate targeted patient population and reasonable eligibility requirements that correspond with that targeted population. Even the most scientifically compelling trial will not succeed unless the population served at the site meets the eligibility criteria. The strategic review might also include evaluating the site's portfolio for overlap, which can result in wasted resources. Many sites attempt to reduce overlap by offering only one trial for each disease stage and type, thus reducing competition for the same patient population. This strategy varies on the basis of the needs and size of the research site.

Efforts to improve efficiency will result in better utilization of resources and ensure a solid infrastructure for the continually advancing field of cancer research. There are many ways to promote efficiency and improve infrastructure at research sites, and this article provides only a brief introduction to this important topic. We encourage readers to review the OEWG report for additional ideas related to efficiency and to learn more about the timelines that will affect NCI-sponsored clinical trials starting in January 2011.

Suggest future topic ideas for the series and provide your feedback by sending an e-mail to researchresources@asco.org.

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