CE Objectives and Evaluation Form to appear on page 8.

CE SERIES

Phase III and IV Clinical Trials: What You and Your Patients Need to Know

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In the October "Cancer: Caring and Conquering" column, phase I and phase II clinical trials were discussed (Yoder, 2005). In this column, an overview of phase III and IV clinical trials, as well as some important information about future direction of clinical trial research, will be provided.

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Note: This column is made possible through an educational grant from C-Change, a Washington, DC, based organization comprising the nation's key cancer leaders from government, business, and nonprofit sectors. These cancer leaders share the vision of a future where cancer is prevented, detected early, and cured or is managed successfully as a chronic illness. The mission of C-Change is to leverage the combined expertise and resources of its members to eliminate cancer as a (major) public health problem at the earliest possible time. C-Change is both a forum and a catalyst for identifying issues and major challenges facing the cancer community and for initiating collaborative actions to complement the efforts of individual C-Change members. Medical-Surgical nurses are invited to learn more about this important organization by visiting www.ndoc.org

Phase III Clinical Trials

In phase III clinical trials, the goal is to compare a new therapy to a standard therapy. A new therapy arrives at phase III testing if it has demonstrated significant efficacy in phase II trials. A drug may be compared to standard therapy as a single agent or as part of a multi-drug/therapy protocol. Each treatment being tested in the trial is called a *study arm* and patients typically are assigned randomly to one of the study arms. The standard trial design for phase III studies is a prospective, randomized trial. In some two-arm studies, the participants receiving the standard of care are placed on the *control arm* and participants receiving the new therapy are assigned to the *treatment arm.* Subjects do not have a choice of which arm they are placed in or what treatment they will receive. Therefore, assignment of the patients is not biased by knowledge of specific demographic or clinical characteristics. Instead, both known and unknown prognostic factors are randomly distributed, allowing the results to be interpreted as being due to the treatment intervention instead of being due to random variation. A randomized design is important in these trials because it allows for the detection of small, but significant differences between treatment regimens (McCabe, 2004).

Because phase III trials require hundreds to thousands of volunteers to answer the research question adequately, they most often take place in multiple facilities nationally, including community settings (referred to as *multicenter* or *multi-site* trials). Patients are candidates for phase III trial participation if they have measurable disease, adequate organ function, little or no prior cancer therapy, and a good performance status. In the future, the evaluation of agents in phase III trials likely will include several relevant tumor types in the same trial because the eligibility will be determined by the molecular characteristics of the tumor (McCabe, 2004). The effect of the treatment on the molecular target would guide the trial process and be the main effect evaluated. This approach would allow the findings to be relevant to the entire population having the same molecular target, rather than to just a single tumor type.

In many clinical trials, quality of life (QOL) also is assessed as part of the evaluation of endpoints. Patients are typically asked to complete a QOL questionnaire prior to beginning the clinical trial, at various times during the treatment period, and

when treatment is completed. Quality of life typically includes multiple domains consisting of physical, interpersonal, psychological, and spiritual functioning. Sometimes a treatment may not demonstrate objective improvement in the disease when compared to standard therapy, but it may improve a patient's QOL. In oncology patients, improvement in QOL may be a significant finding that the U.S. Food and Drug Administration (FDA) takes into consideration when evaluating a drug for approval.

Phase IV Trials

After approval of a specific agent or treatment regimen by the FDA, additional studies *(post-marketing studies)* may be conducted or even required. The purpose of phase IV trials is to acquire new information about any risks or side effects that were identified previously. Such studies have been useful in identifying potential issues with agents/regimens that were not discovered during early-phase trials (McCabe, 2004; Mulay, 2002).

Reporting Results of Clinical Trials

Some reviews have claimed the quality of reporting of clinical trials is poor (Begg, 1990; Pocock, Hughes, & Lee, 1987). In 1985, Simon and Wittes developed a set of guidelines for reporting clinical trials. These guidelines, which were adopted by several oncology journals, consist of the following 8 points:

1. Authors should briefly discuss the quality control methods to ensure the data are complete and accurate.
2. All patients registered on the study should be accounted for.
3. The study should not have an inevaluability rate of greater than 15% for major study end points.
4. In randomized trials, the report should include a comparison of survival and other major study end points for *all* eligible patients as randomized, with no exclusions.
5. The sample size should be large enough to establish or conclusively rule out the existence of effects of clinically important magnitude. The adequacy of sample size should be demonstrated with confidence intervals. The report also should indicate how many interim analyses were done and how the decisions to stop accrual and report results were made.
6. Claims of therapeutic efficacy should not be made based on nonrandomized phase II trials, unless the disease is so rare or the prognosis is so poor that properly controlled randomized trials are not possible. In instances where randomized trials are not possible, nonrandomized trials should use explicit historical controls for which comparability of patients can be thoroughly evaluated.
7. The patients studied should be described as thoroughly as possible. Applicability of conclusions to the general population of patients should be addressed.
8. The methods of statistical analysis should be described with enough detail that a knowledgeable reader could reproduce the analysis if the data were available (Simon, 2005).

Access to Clinical Trial Information

A growing amount of information available on the Internet concerning clinical trials. An Internet query on November 17, 2005, yielded 5,460,000 results in response to the key words "clinical trials." Clearly, more information is not always better because patients and family members can be overwhelmed by the amount of information available about clinical trials. Therefore, some of the most informative and medically correct sites concerning clinical trails are provided here. Not all of these sites focus on cancer trials; for example, http://www.clinicaltrials.gov provides information about all types of clinical trials and responds to the type of problem typed into the key problem area. Other excellent sites are listed in Table 1.

Special Access Programs: Nonclinical Trial Access to Experimental Agents

Specific programs are available to people seeking access to agents being evaluated in clinical trials, even if they are not eligible for the trial. Such programs are called the *special access programs.*

Treatment Referral Center (TRC). This is available through the National Cancer Institute (NCI) to provide access to experimental agents when a patient population is identified for which an investigational agent should be available. The NCI develops and provides the TRC protocol to the identified cancer centers, which can then offer it to the appropriate patients (McCabe, 2004).

Group C Program. This program is offered by the NCI to allow access to agents that have reproducible activity in one or more types of cancer and that are likely to alter the pattern of the treatment of the disease. Each Group C protocol has eligibility and reporting requirements, and the agents must be administered by properly trained physicians. Group C protocols cannot require specialized care facilities and the drugs are provided free of charge. Additionally, the Center for Medicare and Medicaid Services (CMS) pro-

Table 1.
Clinical Trial Information Web Sites

U.S. National Institutes of Health
http://clinicaltrials.gov

Thomson Centerwatch
http://www.centerwatch.com

Pharmaceutical Research Plus, Inc.
http://www.clinicaltrials.com

National Cancer Institute
http://www.cancer.gov/clinicaltrials

C-Change
http://www.ndoc.org/clinical_trials/default.asp

TrialsCentral
http://www.trialscentral.org/

vides coverage for beneficiaries of care associated with Group C therapy (McCabe, 2004).

Expanded Access Program. These programs are available for a limited number of well-studied investigational agents when substantial evidence indicates that the agent has significant activity against a specific type of cancer and may provide benefits to people with that cancer. This program allows a larger group of people to be treated with the therapy before the FDA approval process has been completed. The sponsor of the investigational new drug (IND) must apply to the FDA to make the therapy available through the expanded access program. The sponsor must provide adequate evidence from completed trials showing that the therapy may be effective to treat a specific type of cancer and that the drug does not have unreasonable risks (McCabe, 2004).

Special Exception (Compassionate Exception/Use). In this program the patient's physician must contact the study sponsor and provide the patient's medical information and treatment history. Requests to receive clinical trial agents are then evaluated on a case-by-case basis and the FDA must approve each request to administer the agent outside a clinical trial. Accessing an agent under this program requires a belief that the agent will prolong survival or improve the patient's QOL (McCabe, 2004).

Directions for the Future

Clinical trials programs for the future need to accommodate interventions that are developed for and directed to specific genetic, molecular, and cellular mechanisms. Von Eschenbach (2005) has indicated clearly that designed interventions for defined populations at risk that includes the profiling of the patient and the tumor will become the standard of care. The National Cancer Program has partnered with the FDA to determine what would constitute an ideal clinical trials/oncology clinical research system. Creating a seamless national clinical trials infrastructure across the spectrum of NCI-supported research groups will accelerate the completion of the trials, increase patient safety, and speed up the development and delivery of novel detection and intervention regimens (Von Eschenbach, 2005).

To that end, the National Cancer Advisory Board (NCAB) of the NCI accepted 22 strategic proposals for revamping the NCI's cancer clinical trials system and a 5-year implementation plan to accomplish the changes. The NCAB is an oversight group that makes recommendations to the NCI; the NCI is part of the National Institutes of Health (NIH), the biomedical research arm of the federal government. The NIH is an agency of the U.S. Department of Health and Human Services. Advances in molecular medicine were the driving force behind the Clinical Trials Working Group (CTWG) recommendations. These advances offer enormous potential to improve cancer clinical practice by advancing beyond the toxic treatments of the past, but they also create new challenges for the design and conduct of cancer clinical trials.

The new blueprint for the NCI's clinical trials enterprise was submitted to the NCAB by the CTWG, a broad-based group convened in 2004 by NCI Director Andrew von Eschenbach, MD, to provide advice about optimizing the NCI-supported clinical trials system. By accepting the report, the NCAB endorsed the CTWG's recommendations to NCI (NCI, 2005). Clinical Trials Working Group members representing industry, professional associations, and institutions performing clinical investigations answered questions for NCAB members

in a 77-page report called "Restructuring the National Cancer Clinical Trials Enterprise." "This enormous potential for more specific cancer treatment, coupled with the complexity of evaluating new, highly specific agents, requires robust clinical trial designs," said Howard Fine, MD, chief, Neuro-Oncology Branch, Center for Cancer Research, who co-chaired the CTWG (NCI, 2005). Oncology clinical researchers believe the development of such trials will necessitate comprehensive information sharing and close collaboration among clinical researchers and basic and translational scientists, as well as scientists developing modern molecular diagnostic and imaging techniques. The report includes an implementation plan with a timeline and budget for each initiative, as well as a recommendation that a formal evaluation system be developed to assess the success of the restructuring effort over time.

The CTWG initiatives are organized into five categories, and in each section, the initiatives are organized into two types. New initiatives propose fundamental and significant changes in the operation of the NCI clinical trials system. Initiatives propose expansion or enhancement of activities already underway within NCI. The five categories, with new initiatives, follow.

Coordination Initiatives

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

Prioritization/Scientific Quality Initiatives

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

Standardization Initiatives

1. Create, in partnership with the extramural cancer research community, a national cancer clinical trials information technology infrastructure fully interoperable with NCI's Cancer Bioinformatics Grid to improve cost effectiveness and comparability of results across trials and sites.
2. Together with industry and the FDA, develop standard case report forms incorporating common data elements to improve information sharing among cancer researchers and optimize data requirements.
3. Build a credentialing system for investigators and sites recognized by the NCI and industry to allow faster trial initiation and keep the clinical research community abreast of legal, safety, and regulatory changes.
4. Develop commonly accepted clauses for clinical trial contracts with industry to reduce the lead-time needed to open trials.

Operational Efficiency Initiatives

1. Restructure the phase III funding model to promote rapid patient accrual rates and cost-effectiveness.
2. Reduce institutional barriers to timely trial initiation.
3. Increase patient and public awareness and understanding of clinical trials.
4. Increase minority patient access to clinical trials to improve the participation of underserved and underrepresented populations.
5. Promote adoption of the NCI Central Institutional Review

Board facilitated review process to reduce the time and resources needed to open trials at individual sites.

Enterprise-Wide Initiatives

1. Create a Clinical Trials Oversight Subcommittee of the NCAB to advise the NCI director on conduct of clinical trials across the institute.
2. Develop a coordinated NCI organizational structure to manage the entire clinical trials enterprise supported by the institute.

More information about the CTWG can be found at http://integratedtrials.nci.nih.gov. The full report can be found at http://integratedtrials.nci.nih.gov/ict/CTWG_report_June2005.pdf.

The issues surrounding clinical trials can be complex, but work is occurring to attempt to make clinical trials more available to patients that could benefit from them. Of equal importance is that major initiatives are underway to make the results of clinical trials more readily available to clinicians in order to implement evidence into practice quicker. In the next "Cancer: Caring and Conquering" column, issues of patient decision making and informed consent concerning clinical trials will be presented. ■

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Answer/Evaluation Form: MSN J520

Phase III and IV Clinical Trials: What You and Your Patients Need to Know

This test may be copied for use by others.

COMPLETE THE FOLLOWING:

Name: _____

Address: _____

City: _____State: _____Zip:_____

Preferred telephone: (Home)_____ (Work)_____

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Answer Form:

1. If you applied what you have learned from this activity into your practice, what would be different?

_____

_____

_____

_____

Evaluation	Strongly disagree				Strongly agree
The offering met the stated objectives.					
2. By completing this activity, I was able to meet the following objectives:					
a. Describe phase III and IV clinical trials.	1	2	3	4	5
b. List guidelines for reporting of clinical trials.	1	2	3	4	5
c. Describe an ideal clinical trial/oncology clinical research system.	1	2	3	4	5
3. The content was current and relevant.	1	2	3	4	5
4. The objectives could be achieved using the content provided.	1	2	3	4	5
5. This was an effective method to learn this content.	1	2	3	4	5
6. I am more confident in my abilities since completing this material.	1	2	3	4	5

7. The material was (check one) ___new ___review for me

8. Time required to complete the reading assignment: _____minutes

I verify that I have completed this activity (Signature):

_____

Comments

_____

_____

_____

Objectives

This educational activity is designed for nurses and other health care professionals who care for and educate patients and their families regarding cancer clinical trials. For those wishing to obtain CE credit, an evaluation follows. After studying the information presented in this article, the nurse will be able to:

1. Describe phase III and IV clinical trials.
2. List guidelines for reporting of clinical trials.
3. Describe an ideal clinical trial/oncology clinical research system.

CE Instructions

1. To receive continuing education credit for individual study after reading the article, complete the answer/evaluation form to the left.

2. Detach and send the answer/evaluation form along with a check or money order payable to **AMSN** to *MEDSURG Nursing*, CE Series, East Holly Avenue Box 56, Pitman, NJ 08071–0056.

3. Test returns must be postmarked by December 31, 2007. Upon completion of the answer/evaluation form, a certificate for **1.2** contact hour(s) will be awarded and sent to you.

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