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EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Describe the three phases of clinical trials
- Understand basic statistical concepts used in cancer research trials: *P* value, confidence interval, relative risk, and hazard ratio
- Describe issues that concern patients about participation in clinical trials

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The methods and terminology of cancer trials: A review

Donald R. Fleming, MD

STATEMENT OF NEED/PROGRAM OVERVIEW

Oncology nurses and nurse practitioners assist in evaluating and treating cancer patients on a daily basis. If clinical trials are a part of the practice, these clinicians will be expected to assist with forms, informed consents, data recording, and explaining the study to prospective participants. It is important that nurses understand the basics of cancer research.

CE INFORMATION

Title: The methods and terminology of cancer trials: A review

Release date: June 15, 2010

Expiration date: June 15, 2012

Estimated time to complete this activity: 30 minutes

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Target audience: This activity has been designed to meet the educational needs of registered nurses and nurse practitioners involved in the management of patients with cancer.

Media: Journal article and Web sites (mycme.com; OncologyNurseAdvisor.com; nphealthcarefoundation.org)

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The methods and terminology of cancer trials: A review

Oncology nurses involved in clinical trials must understand the basics of cancer research and their practice's studies to better carry out the research.



DONALD R. FLEMING, MD

Clinical research, also known as *clinical trials*, is a necessary part of every field of medicine. Clinical trials have contributed an enormous amount of data and considerable knowledge to cancer treatment. Although cancer research originates in a laboratory that is filled with test tubes and laboratory animals, human volunteers are the key to determining the absolute clinical benefit of new cancer treatments and techniques.

PHASE I, II, AND III TRIALS

Clinical trials for cancer are designed by experts with knowledge of specific types of cancer. Once the trial has been designed, it undergoes scrutiny by a *scientific review committee*, which typically resides at the institution of the trial's origin. It is then submitted to a patient advocate-oriented *institutional review board* made up of both laypersons and professionals, who decide whether the trial as designed will inform the patient completely about all the possible consequences and benefits of the trial, as well as about existing alternative treatments. This information is put together into what is called an *informed consent* document, which participants must sign to indicate that they have been fully informed about the trial and their risks and responsibilities.

Clinical trials are then designated as being one of three types: Phase I, Phase II, or Phase III. The type of trial is determined by the trial's design. **A Phase I clinical trial** involves testing new treatments or medicines for the sole purpose of determining whether patients can tolerate the medication. In other words, the prime concern is determining degree of toxicity. Because this is the initial trial, patients are not expected to improve while receiving the medication, but improvements can occur. This form of cancer research will often consist of a series of dose escalations to find what is known as the *maximum tolerated dose*, or *MTD*. The MTD is the highest dose of the studied therapy that can be tolerated by the subjects.¹

After a Phase I study has determined that a medication or treatment is safe enough to be used by patients, a **Phase II study** then determines whether the treatment or medication is effective.² In some situations, a trial can be both Phase I and Phase II at the same time. Phase II trials often consist of a few dozen patients.

There has been some recent interest among cancer researchers in what is known as a *randomized Phase II approach*. In this approach, the study subjects are divided into two groups: the experimental group and the control group. This type of trial has been controversial because it gives the impression that enough subjects are being studied for a comparison of treatment effectiveness to be made, when the numbers being studied are in fact not large enough to make any statistical statement of validity. A randomized Phase II study is often done to see if pursuing a more meaningful Phase III trial design would be worth the expense.

Phase III trials are a continuation of Phase II trials in that once a medication has shown evidence of effectiveness, it is often compared to what is considered the standard treatment or treatments to determine whether the new medication is an improvement. In Phase III trials, all patients receive a standard treatment for their particular cancer if a standard treatment exists. In some cases, this standard treatment may be what is known as *best supportive care*. All patients are randomized into two (or more) groups, which are commonly referred to as *arms* of the study. In many situations, one arm will receive the standard treatment and/or the new treatment being tested. This group may also be called the *active group*. The other arm—often referred to as the *control group*—will receive the standard treatment and/or a placebo. Neither the clinician nor the patient knows who is in which arm of the study.

After a Phase III trial has concluded and the data have been analyzed, medications or treatments go before the FDA for consideration of approval for treatment of the particular

disorder for which the trial was designed. Sometimes this approval can be based on Phase II data if the benefits of the new treatment are obvious.

UNDERSTANDING STATISTICS

Statisticians are an intricate and essential part of designing a Phase III trial. They must prospectively determine how many patients need to be compared to show a clinical significance. This is often referred to as the **power** of the trial. Power will be described in terms of the percent chance a trial has of showing a certain percentage of difference. A trial having a 90% chance of demonstrating a 20% difference is a common goal of a trial's power.

The **P value** is also a common term discussed in Phase III trials and refers to the statistical measure of whether the trial results can demonstrate that there is a different outcome among the compared groups. A *P* value less than .05 ($P < .05$) is often the goal and means that there is less than a 5% chance that the results could have occurred by chance.

For example, suppose that researchers want to study whether chemotherapy drug A is more effective than chemotherapy drug B. Before the trial is started, statisticians must deter-

After a Phase III trial has concluded and the data have been analyzed, the medication goes before the FDA for consideration of approval.

mine how many patients the study must include to show with reasonable (90%) certainty that the treatments have a 20% difference in outcome. This would be the power of the study. After the study is completed, statistical analysis of the data will determine whether the difference seen between chemotherapy drugs A and B had less than a 5% chance of occurring by chance ($P < .05$).^{3,4}

Another term is **confidence interval** or **CI**. The CI is the spread of results that should be considered as the potential actual impact of a treatment. The desire is to have a CI of a narrow range and to have ranges of results that do not demonstrate any overlap between the studied groups or arms. If the CI does overlap, it means that the two groups may not be different in some situations despite the final results demonstrating a difference.

To return to our example study comparing chemotherapy drugs A and B, 95% of the individual patient outcomes would be included in the CI. If only a few patients are studied, the

95% CI might include results that are very different from one another, producing a CI of wide range; in a large trial, however, many of the patients are likely to have similar results, and thus the CI will be of narrower range. If CI overlap is seen when the two treatments are compared, this means that for some patients, the two treatments showed no difference in outcome. If only a small number of patients are included in a trial comparing two treatments, the results may show a significant difference; but the CI may be so broad that the two results overlap, and thus the results may not be different at all for several patients.

Clinical trials can have what are called **alpha (type I)** and **beta (type II)** errors. An alpha error is present when a trial shows a difference that really does not exist. This is referred to as a *false positive*. A beta error is just the opposite and is present when a trial shows no difference in the treatments when one actually exists. This is referred to as a *false negative*.

Patients may not understand that trials are designed both to avoid the use of an inferior treatment and to determine the best treatment.

These errors are simply the results of outcomes defying the odds of numbers that were determined to be necessary in order to carry out a comparison between two treatments or outcomes.⁴ The only way to minimize the chances of both types of errors is to increase sample size, which may or may not be feasible.

In clinical trials, **relative risk (RR)** is the risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the likelihood of the event occurring in the control group versus the experimental (or noncontrol) group. If the event is less likely in the experimental group, then the RR is less than 1; if the event is more likely, the RR is more than 1. An outcome is more likely if the RR is greater than 1 and less likely if the RR is less than 1. The outcome might be a bad thing (such as a toxicity reaction) or a good thing (a more effective treatment).

Another often used term in statistics, and similar to RR, is the **hazard ratio (HR)**. In cancer trials, HR typically refers to survival differences between two or more groups being compared. The HR is useful when the risk is not constant with respect to time as it uses information collected at different times. The term is typically used in the context of survival over time.

As an example, if the HR is 0.5, then the relative risk of dying for one group is half the risk of dying for the other group. HR may refer to *overall survival* or to other forms of survival, such as *disease-free* or *progression-free* survival. An HR of 1 corresponds to equal treatments; an HR of 2 implies that at any time, twice as many patients in the active group are having an event proportionately compared with the comparator or control group. An HR of 0.5 means that half as many patients in the active group have an event at any point in time compared with placebo.

PATIENT CONCERNS

Patients in clinical trials sometimes express concern that they might be receiving inferior treatment if they learn that they were receiving the placebo and not the experimental drug being tested. They also worry that the “new” therapy might not be as good as the standard treatment for their disease. However, trials are designed both to avoid the use of an inferior treatment and to determine the best treatment. Clinical trials have built in periodic checks and balances that constantly monitor and analyze patient progress. If one group is determined to be doing significantly better than another group in a phase III trial, the trial is discontinued, and in some cases patients are offered the more effective medication or treatment. This is because the new treatment has demonstrated superiority to previous treatments early on. Likewise, if a particular treatment has shown that the risks outweigh the potential benefit, the study is terminated. In addition, new treatments sometimes look promising in a Phase II study, based on past nonstudy patient experiences, but when all patients in a Phase III trial are analyzed, the results indicate that those who did not receive the new treatment did as well as those who did receive it.

Furthermore, patients who participate in clinical trials often have a better outcome simply because they are



The NIH registry of clinical trials

participating in a trial. The explanation may be that these patients are seen by health care providers more frequently and are monitored even more closely than they would have been otherwise. Not only are their physicians, nurses, and others closely observing their progress, the company sponsoring the research regularly reviews their medical

Most of the money spent on cancer research goes toward studying the biology or mechanisms of cancer, not for testing specific treatments.

information and alerts the health care team to any problems they might find. These advantageous aspects of participating in a trial are important to explain to patients who may worry a great deal over their inability to control which treatment they receive.

Many patients ask about insurance reimbursement for coverage of clinical trials. They fear that insurance providers will consider the trial experimental and will not reimburse the physician or other health care providers for the therapy. Medicare has recently begun to cover clinical trials, and other third-party payers have found it is actually beneficial to support participation in clinical trials to achieve better and potentially less expensive outcomes.⁵ It is unusual today for any type of health care provider to decline reimbursement to a patient participating in a clinical trial. Patients should also be reassured that approval from their insurance will be secured before they proceed with the study. Furthermore, treatments or medications that are not FDA-approved and cannot be billed for are typically covered by the sponsors of the study.

HIPAA (Health Insurance Portability and Accountability Act) regulations have raised concerns among those involved in cancer research about how to adhere to HIPAA rules and regulations while remaining involved in cancer clinical trials. HIPAA rules have adversely affected interactions between research institutions (such as by making data sharing more difficult) and have added an extra layer of bureaucracy and regulation.⁶

FUNDING CLINICAL TRIALS

Most of the money spent on cancer research in both the United States and Europe is spent primarily on studying the biology or mechanisms of cancer. Lesser amounts are spent on the development of new clinical treatments to be

tested in patients and on the establishment of measures to prevent the development of cancer. The difference between the funding of cancer research in the United States and in Europe is dramatic, however. The United States spends several times more per person on cancer research than does any of the wealthiest nations in Europe.⁷ The causes for this disparity may be rooted in the different health care systems in the various countries and in the amount of nongovernment funds available for research.

The amounts various countries spend on cancer research may seem to be less important in today's world of rapid communication and information sharing. It remains true, however, that countries with more active research programs tend to provide improved cancer treatments more rapidly to the community of patients. The United States should be proud of our activity in the fight against cancer and our contribution to this area of medicine.

The world also owes a debt of gratitude to the cancer patients who participate in clinical trials. While these patients generally do so in hope for a better outcome for themselves, they also are contributing information to oncology research that will benefit future cancer patients. Their altruism has allowed many cancers to be cured and most to become manageable diseases. ■

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