

FACT SHEET

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Cancer Clinical Trial Design and Endpoints

Cancer is the second largest killer of individuals in the United States, surpassed only by heart disease. The American Cancer Society estimates that in 2010 more than 1.5 million people were diagnosed with cancer and more than 560,000 died from the disease.¹ Despite recent advances in cancer care, there is still a significant need for more treatment options.

To address this need, many private and public institutions focus their research on understanding different cancer types and developing potential medicines. Each new medicine in development in the U.S. must go through a comprehensive clinical trial process that is registered with the U.S. Food and Drug Administration (FDA) to ensure that products approved for patient use are safe and effective.

Clinical Trial Endpoints

A clinical trial is a research study designed to evaluate the efficacy (clinical benefit) and safety profile of a medicine or to validate a diagnostic test. Specific “endpoints” determined at the beginning of the study define the goals of the trial and provide the foundation of the trial design.² Common endpoints used in cancer treatment trials include:

- **Overall survival (OS)** — the length of time a person lives measured from the time of enrollment in a clinical trial until the time of death²
- **Median overall survival (mOS)** — the time at which half of the people enrolled in a clinical study are still alive
- **Progression-free survival (PFS)** — the amount of time during and after treatment that a person lives without the disease worsening (progression)²
- **Median PFS (mPFS)** — the time at which half of the people enrolled in a clinical study are still alive and have not experienced disease worsening (disease progression)
- **Time to progression (TTP)** — the amount of time during and after treatment that a person lives without the disease worsening (progression); TTP does not account for death from worsening disease, whereas PFS does²
- **Complete response rate (CR)** — the percentage of people in whom the cancer is no longer detectable as a result of treatment; a CR does not mean the cancer has been cured³
- **Partial response rate (PR)** — the percentage of people who experience a decrease in the size of a tumor, or in the extent of cancer in the body, of more than 30 percent in response to treatment³
- **Overall response rate (ORR)** — the percentage of people who experience a decrease in the size (or amount for blood cancers) of the cancer for a minimum amount of time; ORR is the sum of the complete and partial response rates²
- **Stable disease (SD)** — cancer that is neither decreasing nor increasing in size or extent³
- **Duration of Response** — time from initial response to therapy until documented cancer progression²

Endpoint definitions vary slightly among groups that use them for different purposes. For example, the FDA may define endpoints that apply to several types of cancer, while trial investigators, those scientists and physicians conducting the research, tailor the definitions for their particular studies.

- All clinical trials have a measure of benefit called the **primary endpoint**, which is decided before the trial begins and is the principal factor determining the trial's outcome.⁴ The primary endpoint is typically the outcome evaluated by the FDA.
- Endpoints other than the primary endpoint are called **secondary endpoints**. For example, a clinical trial may have a primary endpoint of PFS and secondary endpoints of OS, ORR and TTP⁴
- Endpoints can be reported based on all of the people who enter a clinical trial or based on a subset of people with specific characteristics, e.g., sex, ethnic background, extent of disease or the presence of a particular biomarker⁴

Reporting Endpoint Data: Hazard Ratio vs. Median

For endpoints that measure events, like disease progression (PFS) or death (OS), the data can be reported in different ways. The hazard ratio (HR) is a measure of the degree of improvement in the trial's endpoint over the course of the entire study.³ For example, the hazard ratio can help determine the degree to which a cancer medicine reduces the risk of death or of the risk of disease worsening compared to a control group.

The median value, on the other hand, is the middle number in a group of observations.³ For example, the median PFS is the time at which half of the people enrolled in a clinical study are alive and have not experienced disease worsening. The median value is based on a single point in the study and does not take into account all of the data.

Research Stage Can Determine Endpoints

Different clinical trial endpoints have different purposes. Typically, early-stage clinical trials (Phase I/II) evaluate the safety profile and evidence of treatment activity, such as tumor shrinkage. Endpoints for late-stage efficacy studies (Phase III) usually show whether a medicine provides meaningful clinical benefit, such as reducing the risk of the disease worsening (PFS) or improving survival (OS).² After a medicine receives FDA approval, post-marketing studies (Phase IV) may be conducted to gather additional information about a medicine's efficacy, safety profile or optimal use.⁵

Other Elements of Clinical Trial Design

In addition to the endpoints chosen and the stage of the study, other factors in the design of a clinical trial may influence interpretation of the results. Common terms and concepts related to trial design include:

- **Blinded and open-label trials**
 - A blinded trial is one in which the patients involved in the study (single-blinded), or the patients and their doctors (double-blinded), do not know which medicine is being used⁴
 - In an open-label trial both the patients and their doctors are aware of the medicine being used
- **Controlled study**
 - A controlled trial is one that includes a comparison or control group³

- By using a comparator group, it may be possible to accurately gauge the effectiveness or safety profile of a new medicine compared to another³
- **Randomization**
 - People in randomized clinical trials are randomly assigned to one of at least two groups (e.g., treatment or control group)⁴
 - Randomization prevents bias and ensures that factors such as tumor stage, age, race or sex do not influence the results⁴
- **Study enrollment criteria⁶**

Each clinical trial has certain conditions, or criteria, that patients must match before they can enter the study. This requirement is necessary to ensure that the study can answer the questions it was designed to answer. For cancer clinical trials, these criteria often include:

 - The type of cancer
 - The stage (extent)
 - Previous treatments
 - The length of time since last treatment
 - Results of certain lab tests
 - Other medicines a person is taking
 - Other medical conditions
 - Previous history of another cancer
 - A person's activity level (also known as performance status)

Eligibility criteria may be very detailed if researchers believe that a medicine will work best in specific people or types of cancer. Trials with narrow eligibility criteria may produce results that are less widely applicable. The more diverse the trial population, the more applicable the results may be to the general population, especially in Phase III studies.

Learn more about clinical trials by visiting <http://www.cancer.gov/clinicaltrials/education/in-depth-program>.

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