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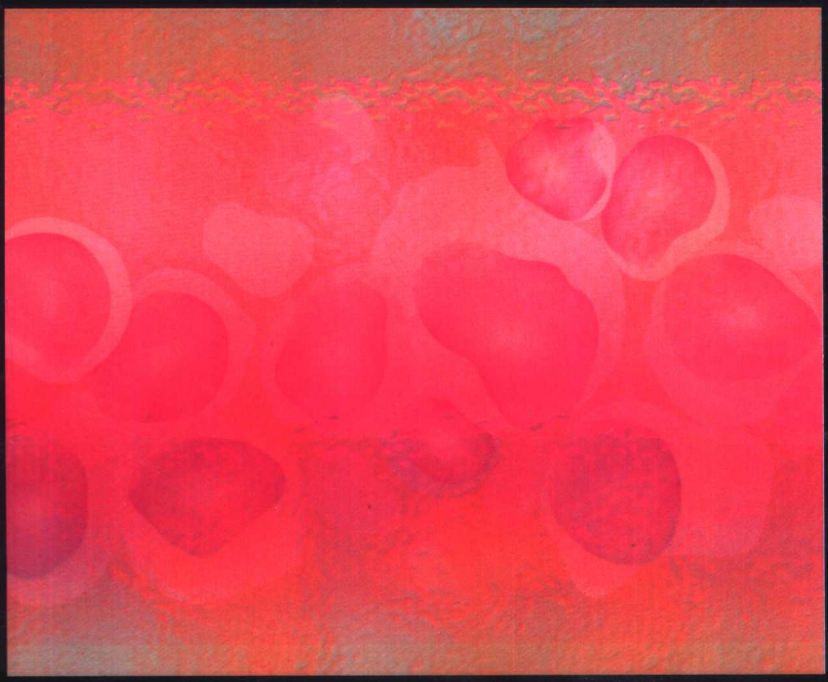
The Washington Manual of Oncology

Department of Medicine Division of Oncology
Washington University School of Medicine
St. Louis, Missouri

配英汉索引

华盛顿肿瘤学手册

Editor
Ramaswamy Govindan
Associate Editor
Matthew A. Arquette



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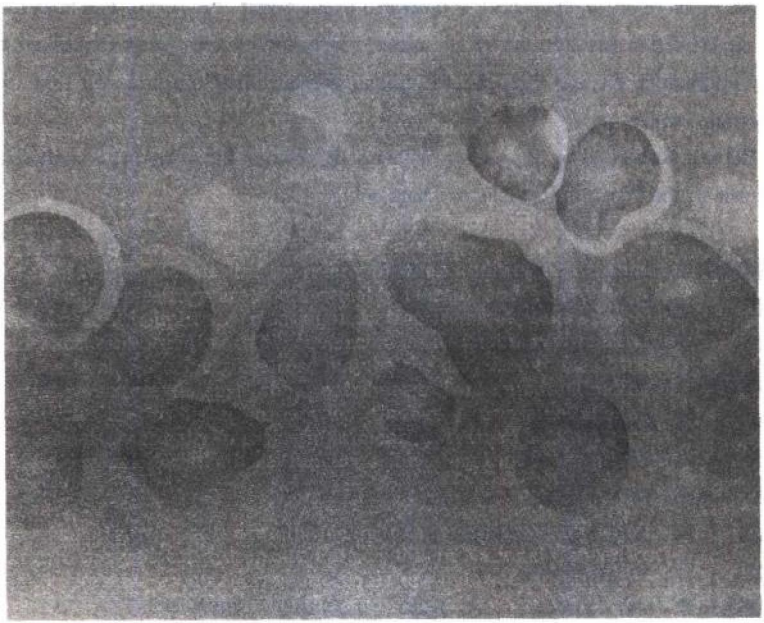

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THIS BOOK IS DEDICATED TO MY PARENTS

Kollengode A. Ramaswamy
Pankajam Ramaswamy

for their selfless sacrifice

PREFACE

These are exciting times in oncology. The novel imaging techniques, improved supportive care, and the availability of several new agents that have novel mechanisms of action hold considerable promise in improving the outcomes of cancer patients. In this era of information overload, it is critically important to have a practical manual that is helpful to physicians taking care of patients with cancer.

The chapters are arranged in a logical order beginning with evaluation of symptoms and proceeding in an orderly fashion through the work-up, staging, and stage-directed therapy, and finally ending with discussion on epidemiology and current focus of research. We have embarked on this first edition of *The Washington Manual of Oncology* to provide a very practical manual that is helpful to medical residents, fellows in training, nurse practitioners, and other practitioners of clinical oncology. Our plan is to publish this book in a timely fashion every two years to keep the information current and up-to-date.

Ramaswamy Govindan, M.D.

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The Washington Manual of Oncology

CONTENTS 目 录

1. PRINCIPLES OF CLINICAL TRIALS

Kathryn M. Trinkaus and J. Philip Miller

I. What is a clinical trial?

Broadly speaking, a clinical trial is the process of testing the effect of any drug, medical or surgical procedure, medical device, or other intervention (collectively referred to here as "treatments") in human beings to determine its efficacy and safety in preventing, alleviating, or curing illness or injury. This requires that there be genuine doubt concerning the benefit of the treatment relative to the best, current treatment (**standard of care**), sometimes referred to as a state of **"equipoise."**

II. Principles of good clinical practice

A. Current definitions of good clinical practice can be found in the **Declaration of Helsinki** (World Medical Association, revised October 2000), the **Belmont Report** (OPRR Report, April 18, 1979), and **Good Clinical Practice: Consolidated Guideline** (International Conference on Harmonisation *Fed Reg* 1997;May 9). In brief, these sources state that the rights, welfare, and ability to make decisions of individual study participants take precedence over possible benefits to collective entities such as science or society. Individual consent is essential and must be fully informed and freely given. The informed consent safeguards the participants' welfare by describing in detail and in nontechnical (e.g., eighth-grade reading level) language the protocol to be followed. It fully informs participants of any known or anticipated risks, benefits, or other aspects of the trial that may affect their willingness to participate.

B. Autonomy. Informed consent also affirms the participants' autonomy by stating their right to withdraw without penalty at any time. The participant gives consent by signing and dating the form. The clinical staff member presenting the consent form answers any questions posed by the participant. The staff member also signs and dates the form. Consent must be voluntary, without restraint, coercion, or fear that future medical care will be compromised. Reconsent is obtained if the trial is amended or new scientific information becomes available that may alter the participants' willingness to be included in the trial.

C. Beneficence and justice. Known or anticipated risks and benefits must be weighed and the trial conducted only if benefits outweigh risks. Investigators are obligated to minimize risks. Participants who bear the risks and inconveniences of participation in the trial must have a fair share in the benefits of improved treatment.

D. Scientific merit. The research questions under investigation must be supported by the best available scientific information, and the trial must be conducted in such a way as to produce sound, scientifically valid results. Study personnel must have skills, education, training, and experience appropriate to their roles. All aspects of the trial must be adequately documented and available for monitoring or auditing as needed.

III. Initiating a cancer clinical trial

A. What is the question being asked? The first steps are identification of the scientific question(s) to be addressed, formulation of **research hypotheses,** and definition of **study objectives. Prevention trials** are concerned with health promotion or prevention of cancer in those not previously diagnosed with cancer and with the prevention of new primary tumors in persons previously diagnosed with cancer. **Diagnostic trials** focus on means of better identifying cancer, especially on early detection. **Therapeutic trials** are concerned with alleviation or cure of preexisting cancer.

B. **How will the question be answered?** Clinical trials may be organized in several ways. A **retrospective trial** collects data on events or responses that have occurred before its initiation, whereas a **prospective trial** follows up participants and measures end points at fixed times or as relevant events occur. Trials may include both retrospective and prospective components or a combination of preventive, diagnostic, and therapeutic aims. The ultimate goal may be to determine whether there is a **difference** in effectiveness of treatments. Alternatively, the trial may attempt to determine whether the effects of two treatments differ by less than a clinically relevant, maximal allowable amount, or are **equivalent.** A **cross-sectional trial** gathers data from each participant during a brief interval, whereas a **longitudinal trial** measures the same quantities repeatedly from each participant over an extended time. Participants in a **parallel trial** study group may receive a single treatment before their results are compared, or participants in each group may **cross over** and receive the other's treatment before comparison within and between study groups. If participants cross over to receive a second treatment, a **washout** or rest period is often included to ensure that the effect of the first treatment has ceased before the second begins.

C. **How many institutions will be involved?** Small trials are often carried out at a single institution. If large numbers of participants are needed or if the cancer of interest is rare, then several institutions may collaborate in a multicenter trial. The **National Cancer Institute Cooperative Group** program currently supports about a dozen cooperative oncology groups, each with an organizational framework for the conduct of multicenter clinical trials. At this time, cooperative group trials involve 8,000 researchers at 1,500 institutions and enroll more than 20,000 participants each year in clinical trials.

D. **What are the end points being studied?** Once the objectives are clearly stated, the next step is to choose measurements of the effects of interest, or **end points.** If these cannot be measured directly, then careful consideration is needed to find the best available surrogates. Informative study end points are clearly related to the study hypotheses and objectives, unambiguously measurable with minimal error, and available within a reasonable period. Information-rich measures are preferable, those that finely discriminate between degrees or states of the phenomena of interest. **Common clinical end points** in oncology trials may include survival or time to key events or response rates:

1. **Complete response** is the percentage of patients who have complete resolution of tumor lasting at least 4 weeks.
2. **Partial response** is defined as a 50% decrease in the sum of the products of all measurable sites of disease (as measured by physical examination or radiographs) with no new sites of disease.
3. **Progressive disease** is defined as a 25% increase in the sum of the product of all sites of measurable disease or one or more new sites of disease.
4. **Stable disease** is that which does not meet the definitions for response or progression.
5. **Overall response** is the sum of partial plus complete responses. Stable disease or tumor regression may be considered responses to treatment of very aggressive cancers.
6. **Event-free survival** is the time from a clinically significant event such as diagnosis, treatment, or transplant until some defined event, such as overall survival, disease-free or progression-free survival, time to identification of distant metastases, or local recurrence-free survival. These times may be expressed by a median for the group or a percentage at a particular time point (e.g., 1 year or 5 years).

IV. **Designing the trial**

A. **Study population.** Equally important is defining the **target population,** which is that part of the human population to which the results will be

applicable in a clinical setting. The **sampling frame** is that part of the target population from which the study sample will be drawn. The process by which study participants are identified and recruited is the **sampling strategy.** A sound sampling strategy ensures that end points are represented fully in the study sample so that the results may be generalized to the population that may benefit from them.

B. **Reducing bias.** Bias, which is the difference between a measured estimate and the true value of the quantity being measured, can arise at any stage and must be minimized as far as possible.
   1. **Randomization.** Using a probabilistic sampling strategy, which gives each member of the sampling frame a predetermined chance of inclusion in the study, and randomization, which is the use of a formal probability model to assign participants to treatments, can reduce bias. Use of even/odd numbers, flipping a coin, or manual use of a random-number table is not sufficient. The randomization process must be documented as part of the trial and for audit if necessary. Assignments may be kept in sealed envelopes or be available from a randomization center. A randomized assignment usually is made only after the participant's eligibility is established and his or her informed consent has been given.
   2. **Blinding.** Knowledge of the treatment received by a participant can lead to significant alteration of his or her care and consequent bias of study results. Restricting knowledge of individual treatment assignments can reduce bias arising from differential care of participants. In an **unblinded, unmasked, or open-label** study, assignments are known to study participants, treating physicians, and other study personnel. In a **single-blind** study, either the study participant or the treating physician (usually the former) may be unaware of study group assignments. If both study participants and treating physicians do not know which treatment is being received, the study has a **double blind.** To maintain a double blind, it usually is necessary to extend the blind to other clinical personnel involved with participant treatment, data collection, and data management. Data analysts also may be blinded. Any document linking individuals with treatments must be inaccessible to all blinded study members. Care must be taken to design treatments and controls to be as nearly indistinguishable as possible. Unblinded study personnel must be discrete in discussing study-related information with those who are blinded.
   3. **Other means of reducing bias.** These include careful and consistent implementation of all study procedures by well-trained personnel, including maintenance of blinding (see above) and complete verified data collection. Appropriate data analysis also is needed, controlling for confounding (see later), avoiding non–hypothesis-driven searching for patterns, and including only planned interim analyses (see later). At study end, bias can be reduced by thoughtful interpretation based on observed results and publication of all results, positive and negative, as completely as possible.

C. **Eligibility and exclusion criteria.** The research hypotheses and sampling frame are used to identify characteristics of participants who may benefit from the treatment, the eligibility criteria for the trial. Characteristics of participants who are unlikely to benefit or who may be at unusually high risk if enrolled define the exclusion criteria. Eligibility and exclusion criteria are usually specific to the condition and treatment under study, although the presence of unknown or poorly estimable risks (e.g., pregnant or breast-feeding women and their offspring) also may be a reason for exclusion. Participants should never be included or excluded automatically (e.g., by age, gender, or race/ethnicity) or as a matter of convenience. A consecutive series of participants from a single clinic or practice, even if they represent "all-comers," is biased by the nature of the clinic, its location, the mechanisms of referral, and many other factors. Such a single-institution sample

may not be easily generalized to the target population, and any results may require subsequent confirmation before they are accepted.

D. **Study design.** Once the sample is defined, the study design is written. The design is a plan for assignment of participants to treatment; measurement of study end points; and collection, organization, and analysis of the resulting data. The design ensures that the results produced by the study represent its objectives in an accurate and unbiased manner in all parts of the study sample.

1. **An observational or natural history trial** measures study end points without attempting to relate them to a baseline or alternative treatment. Such uncontrolled studies can be useful when little is known about the condition of interest in the target population. They may be used to collect data on treatment safety and study feasibility, as well as to estimate study parameters for the planning of future, controlled trials.
2. **A controlled study** compares two or more treatments given concurrently under similar conditions. Such a study has at least two **arms,** or participant groups receiving different treatments. The control arm may receive a **placebo,** an inactive or dummy treatment that resembles as closely as possible the experimental one. Alternatively, the control arm may use an **active control,** a different but active alternative to the experimental treatment, usually the current standard therapy. Use of a placebo is ethically justified if there is no established standard of care or known effective treatment under the circumstances that surround the trial. Otherwise, it is unethical to offer any participants less than the standard of care. Patients who have been followed up for the same condition and whose outcomes are known at the outset of the study may be used as a **historical or external controls.** Conclusions from comparison with historical control are questionable because of the many unknown differences, temporal changes, and uncontrolled sources of bias that may occur between the two sets of measurements, however. A **concurrent control,** whether active or placebo, is preferred.
3. **Covariates and confounding variables.** Study hypotheses and objectives usually will make clear which characteristics of the participants, their environment, or the condition of interest may have effects on the end points. These **covariates** often include demographic and clinical characteristics of the participants, aspects of the disease process under study, and any striking features of past or current treatments received. The study hypotheses define how covariates will be included in the analysis and interpretation of study results. If covariates of interest are related to one another, as well as to the study end points, then their interrelations may distort, mask, or **confound** their effects on the outcome measures. If these relations are understood, they can be included in and adjusted for during subsequent analyses. The term confounding also refers to the inability to separate effects of two or more covariates on an end point. If the study arms contain very unequal numbers of participants with differing disease-related characteristics, then it may be impossible to separate the effect of treatment from the effect of the characteristics. For example, if a pulmonary-function study contains one treatment group composed largely of urban residents and another of rural residents, the effect of treatment will be difficult to separate from the effect of residence. To avoid such confounding, assignment of treatments may be **stratified** so each treatment group contains approximately equal numbers of participants with each characteristic (e.g., in a two-arm study, approximately half of all urban residents and half of all rural residents will be randomized to each treatment group). Treatment effects are compared within strata. Participants also may be **matched** on the basis of covariate values (e.g., age, gender, history of treatment). Study end points are the differences observed within the matched sets. Close matching may reduce the number of participants, as appropriate matches become difficult to find. Whether

covariates are effects of interest or factors to be adjusted, their definition and role need careful planning.

4. **New drug development and trial design.** An efficient study design obtains the fullest information possible about study end points from the fewest possible study participants over the shortest possible time. A variety of formal designs are available to maximize information, observe nested effects, or manage the impact of missing data. These are routinely used in a variety of scientific disciplines and are discussed in the references. Drug studies follow steps outlined by the Food and Drug Administration (**FDA**). An Investigational New Drug Application (**IND**) includes the data collected in **preclinical trials** (*in vitro* and animal studies) and early human studies. Human trials begin with a **phase I or dose-finding trial.** In such a trial, a small cohort of patients is treated with a small dose (e.g., 10% of the dose that is lethal in rats) of the drug being studied. This cohort is observed for toxicity. In a classic phase I design, if no unacceptable or dose-limiting toxicities are observed in the first cohort, then another cohort of patients may be treated with a higher dose. This process is continued until toxicity is demonstrated. If only one patient demonstrates toxicity in a cohort, then that group may be expanded and additional patients treated before escalating the dose further. Once dose-limiting toxicity is demonstrated in more than one patient in a cohort, then the trial is completed, and the next lowest dose is considered the maximal tolerable dose (**MTD**) The MTD is recommended for further testing. Although efficacy is not a traditional end point of a phase I trial, patient responses, if observed, may indicate directions for further testing. One problem with the traditional phase I design described here is that too many patients may be treated at low doses, wasting resources by needlessly enlarging the trial and treating patients with subtherapeutic doses. This has led to increasing use of novel phase I designs with more rapid dose escalation. Studies of toxicity, absorption, activity, and clearance of the drug (**safety, pharmacokinetics, and bioavailability**) also are carried out. The participants are usually cancer patients with terminal disease for whom no standard therapy or salvage treatment exists, rather than healthy volunteers, as is often the case in other branches of medicine.
5. **Phase II trials** enroll approximately 20 to 40 participants to investigate the drug's **efficacy** and the better to assess **toxicity** of the drug in a larger group of patients. These may be composed of a single, nonrandomized group or include one or more control groups. Study results may be analyzed before the trial is complete (**interim analysis**) to determine whether there is evidence of **benefit,** lack of benefit (**futility**), or unacceptable **toxicity.** The trial may be stopped for any of these reasons. Interim analyses and early-stopping rules must be planned before starting the trial because testing procedures and significance levels are adjusted to preserve the overall validity of the trial. Results of interim analyses are communicated in an abbreviated form to avoid alteration of treatment and bias of the final study results.
6. **Phase III trials.** If the results are encouraging, larger, multiarm, controlled, randomized phase III trials will compare treatment effects with standard therapy.
7. **Phase IV trials.** After a New Drug Application (**NDA**) has been approved and a drug released by the FDA, additional postmarketing phase IV trials may be carried out to observe treatment effects with long-term follow-up in a broader clinical setting or to examine issues of cost of therapy or quality of life.

E. Power and statistical significance. Once the design is clear, the study power and sample size can be determined. **Power** is the probability of detecting the effects of interest if they exist. The complement of power (1 – power) is the probability of failing to find an effect when one does exist, a **type II**