



June 2008: Cancer Clinical Trials - Basics, Science & Logistics

"What are Clinical Trials? Why are They Important? "

by Grant W. Harrer, MD, Co-Principal Investigator of the Montana Cancer Consortium and Medical Director of the Sletten Cancer Institute, Great Falls, MT

During the next five months, a group of four oncology professionals from around the state will be discussing a series of topics relating to Cancer Clinical Trials. The month of June will be devoted four mini-essays that cover clinical trials basics, the underlying science of the process, and the logistics of clinical trials.

WHAT ARE CLINICAL TRIALS?

They are research studies involving people. Such investigations are occurring in all branches of medicine. However, our specific focus is on "Cancer Clinical Trials" indicating the discussion narrows to research studies involving people relating to a cancer issue. The cancer issue, in a given clinical trial, may deal with treatment, diagnosis, early detection, prevention, supportive care/ quality-of-life, rehabilitation, survivorship, and/or various genetic components.

WHAT IS A CLINICAL TRIAL PROTOCOL?

A "protocol" is a recipe or blueprint for the specific investigation at hand. Based on strict scientific guidelines, each protocol must contain the following:

- . Purpose of the study
- . How many people will participate?
- . Who is eligible to participate?
- . How the study will be carried out?
- . What information will be gathered about participants?
- . Endpoints

WHY ARE CLINICAL TRIALS IMPORTANT?

Cancer clinical trials represent an incredible resource for patients, participants, and society as a whole, though are a poorly understood resource by many. In a nut shell, it is the previous statement that led to devoting the next five months of the Forum to this topic.



Of course, the importance of a given clinical trial relates to the cancer issue being addressed in that trial. Clinical trials provide the means of translating the results of basic scientific research into better ways to prevent, diagnose, or treat cancer.

The clinical trials process is a means of transitioning, from the current standard of care, to a new, better standard of care. In a phrase, cancer clinical trials represent a formal mechanism for making progress in cancer care!

Depending on the study at hand, cancer clinical trials are designed to:

- . Find ways to prevent cancer
- . Find more sensitive ways to diagnose cancer (at earlier stages)
- . Find more effective treatments for cancer
- . Find safer, less toxic treatments for cancer
- . Provide cancer care by leading physicians in the field
- . Provide patients/participants with early access to exciting new drugs and interventions that otherwise are not widely available
- . Provide a chance to help others and improve cancer care

HOW DO LEADING CANCER ORGANIZATIONS VIEW CLINICAL TRIALS?

The American Cancer Society:

"Clinical trials show us what works (and what doesn't) in medicine. They are the best way for doctors to learn what is safe and effective in treating diseases such as cancer."

The National Comprehensive Cancer Network (NCCN):

"The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is strongly encouraged."

The Susan G. Komen Foundation:

"Clinical trials are an excellent way to receive treatment for most women but are not an option for everyone. Even if you are not assigned to receive the new treatment, you will still get the best standard treatment that is available."

Clinical Trials Information (Provided by the Montana Cancer Control Coalition)

Web site: www.cancertrialshelp.org <<http://www.cancertrialshelp.org/>>



A non-profit organization founded in 1997, the Coalition was chartered to increase participation in high-quality cancer clinical trials, thereby accelerating development of new cancer therapies. Today the Coalition offers a full suite of programs and services designed to increase the understanding of cancer clinical trials and boost participation. Close-knit collaborative relationships with healthcare industry partners concentrate on streamlining and promoting cancer clinical trials in both the public and private sectors, enhancing the clinical trials experience for physicians and patients alike.

Web site: www.clinicaltrials.com

Clinicaltrials.com is an internet resource for finding clinical trials in the United States and Canada.

Web site: www.clinicaltrials.gov <<http://www.clinicaltrials.gov/>>

ClinicalTrials.gov provides regularly updated information about federally and privately supported clinical research in human volunteers.

ClinicalTrials.gov gives information about a trial's purpose, who may participate, locations, and phone numbers for more details. The information provided on ClinicalTrials.gov should be used in conjunction with advice from health care professionals.

Website: <http://ctep.cancer.gov> <<http://ctep.cancer.gov/>>

Cancer Therapy Evaluation Program (CTEP)

Website: <http://integratedtrials.nci.nih.gov>
<<http://integratedtrials.nci.nih.gov/>>

Clinical Trials Working Group (CTWG)

Website: www.cancer.gov/clinicaltrials/developments/ncd179n

Centers for Medicare and Medicaid Services (CMS)

Website: www.ctsu.org <<http://www.ctsu.org/>>

Clinical Trials Support Unit

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"Logistics of Clinical Trials-Eligibility, Registration, and Randomization"

by Amanda R. Dinsdale, CCRC, Program Coordinator, Montana Cancer Consortium

Eligibility

To participate in a clinical trial, patients and healthy volunteers must meet certain requirements, which are different for each study. These requirements are termed eligibility criteria. Depending on the questions the research is trying to answer, each clinical trial protocol clearly states who can or cannot participate in the trial. These guidelines are in place to ensure patient safety and accurate and meaningful study results.

Common qualifications for entering a clinical trial include having a certain type or stage of cancer, having been previously treated with a certain kind of therapy or not, general health status, and being in a certain age group.

Registration

Registration occurs after the patient has signed an informed consent form indicating they wish to participate, and after all eligibility criteria have been met. The registration process is a statistical requirement. All patients registered to a clinical trial must be tracked in order to be able to perform statistical analysis of the data gathered. Eligibility data can be linked to subsequent treatment data and follow-up data through the registration process. The registration also identifies the local treating physician and ensures they have met all regulatory requirements necessary to participate in the particular clinical trial. The randomization procedure is initiated at this point.

Randomization

Randomization is a method used to prevent bias in research. Bias is when a trial's results are affected by human choices or systematic factors that are not related to the treatments being tested. Treatment assignments are generated by a computer or table of random numbers at a centralized location away from the institution providing treatment. Participants usually have an equal chance of being assigned to each of the treatment groups within the protocol. If assigned to the control group the patient will get the current standard of care. If assigned to the investigational group the patient will get the treatment being tested. This design can show which treatment is more effective and/or has fewer side effects.

The participant is treated according to the treatment assigned through the randomization process. The protocol document contains information on how the treatment will be given and for how long. It is important the physician and the patient follow the treatment assignment and protocol guidelines. The protocol document will also indicate how long the participant will be followed after treatment has finished. Data collected during the treatment and follow-up phases include things like vital signs, general health assessment, and whether or not the participant's health is getting better. This data is sent to the clinical trial central office where it undergoes statistical analysis. Adherence and compliance to the protocol guidelines ensures quality data is gathered which ultimately leads to establish new and better standards of care.

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"Who Participates in Clinical Trials and Why?"

by Amanda R. Dinsdale, CCRC, Program Coordinator, Montana Cancer Consortium

Who Participates in Clinical Trials

Only 3 percent of adult cancer patients in the United States participate in clinical trials. This is far too few to determine the true effectiveness of many experimental procedures. Why do so few patients participate in clinical trials? Fear is one factor, but studies show that lack of knowledge is the main culprit. In one survey by Harris Interactive, 85 percent of cancer patients were either unaware or unsure at the time of their diagnosis that participation in clinical trials was an option. Of those, 75 percent said they would have been willing to enroll had they known it was possible.

People who take part in clinical trials include those wishing to improve their own health through treatment or supportive care trials and healthy volunteers who seek to advance knowledge about a disease through prevention or genetic trials. Trials can offer hope when existing medical treatments fail, as well as access to promising new treatments and an extra measure of medical attention. In addition, trials recruit patients to find better diagnostic tests or procedures and better ways to screen for and prevent disease. For patients suffering with chronic or terminal conditions, supportive-care trials look to explore ways to improve comfort and quality of life.

To participate, patients and healthy volunteers must meet certain requirements, which are different for each study. Depending on the questions the research is trying to answer, each clinical trial protocol clearly states who can or cannot participate in the trial. These guidelines are in place to ensure patient safety and accurate and meaningful study results.

Individuals interested in participating in a clinical trial should always consult with their physician to understand the personal implications of participating in a clinical trial. Only the treating physician can determine eligibility.

Whenever treatment for cancer is needed, clinical trials may be an option.

The research team, which is made up of physicians, nurses, and research coordinators first explains the trial to the patient. The team explains the trial's purpose, procedures involved, and the potential risks and benefits. The research team will also discuss the patient's rights. The patient has the right to make his or her own decision about whether or not to participate in the trial. If the patient chooses to participate, they have the right to leave the study at any time.

After discussing all aspects of the study, the team gives the patient an informed consent form to read. The form includes written details about the information that was discussed and also describes the privacy of personal records. By signing this form the patient is indicating that they wish to participate in the clinical trial.

It is important that patients be well informed and feel confident and secure about participation. As a treatment option, a clinical trial has possible benefits as well as risks, as does any medical treatment. Before deciding to participate, patients should talk with their doctors, family members, and the research team. When the decision is made the patient should be able to answer the following questions. The answers to many of these questions will have been discussed with the doctor and research team but may also be found in the informed consent form.

- * What is the purpose of the study?
- * What is required of me?
- * What is my role in the study -- am I a healthy volunteer or a patient volunteer?
- * Will the study directly benefit me?
- * Will the study benefit others?
- * Are there risks? If so, what are they and what are the chances that they will occur?
- * What discomforts are involved?
- * What is the total time involved?
- * Are there other inconveniences?
- * Have I discussed participation in the study with those who are important to me, such as family and friends?
- * Do I wish to participate in this study?

Why Participate in a Clinical Trial

Participation in clinical trials can be beneficial. Clinical trials offer cutting-edge treatment options not readily available to the general public.

If a new treatment is proven to work, those first to benefit are those taking part in that clinical trial. By looking at the pros and cons of clinical trials and other treatment choices, the patient is

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playing an active role in their health care. Participation in clinical trials can benefit the patient directly but also provides the chance to help others and improve cancer treatment overall. Altruism plays a large part in this decision for many people. The act of doing something for the greater good can give a sense of satisfaction and personal gratification.

There are a number of ways to find information about participating in a clinical trial. The best first step is to consult with your physician. In addition there are a number of clinical trials websites you can search to find clinical trials available in your area.

Web site: www.clinicaltrials.com <<http://www.clinicaltrials.com/>>

Clinicaltrials.com is an internet resource for finding clinical trials in the United States and Canada.

Web site: www.clinicaltrials.gov <<http://www.clinicaltrials.gov/>>

ClinicalTrials.gov provides regularly updated information about federally and privately supported clinical research in human volunteers. ClinicalTrials.gov gives information about a trial's purpose, who may participate, locations, and phone numbers for more details. The information provided on ClinicalTrials.gov should be used in conjunction with advice from health care professionals.

www.mtcancer.org <<http://www.mtcancer.org/>>

Montana Cancer Consortium is a nonprofit organization whose mission is to bring state-of-the-art cancer treatment and prevention to Montana and Northern Wyoming through clinical trials sponsored by the National Cancer Institute.

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"The Clinical Trials Process: Structure & Science "

by Grant W. Harrer, MD, Co-Principal Investigator of the Montana Cancer Consortium and Medical Director of the Sletten Cancer Institute, Great Falls, MT

Although oncology care in general and oncology clinical trials specifically do involve interventions other than drugs, this essay will deal specifically with drug development. Much of the process does apply to other areas of development. Some of the information summarized here has been provided by Dr. Patrick Beatty, a clinical trial investigator at Montana Cancer Specialists in Missoula.

WHAT IS THE SCIENTIFIC METHOD?

It is a systematic process to objectively move from a question to an answer, as follows:

1. Define the question
2. Gather information and resources (observe)
3. Form hypotheses
4. Perform the experiment and collect data
5. Analyze the data
6. Interpret the data and draw conclusions that serve as a starting point for new hypotheses
7. Publish the results
8. Retest (frequently done by other scientists)

WHAT IS THE DRUG DEVELOPMENT AND APPROVAL PROCESS IN THIS COUNTRY?

It is also a series of steps, both scientific and regulatory, as follows:

1. Basic science (laboratory work) . see details below
2. Preclinical testing (animal models) . see details below
3. IND (Investigational New Drug) application filed with the FDA (Food and Drug Administration)
4. Clinical trials process . see details below
5. NDA (New Drug Application) filed with the FDA
6. FDA validates the claim and approves the drug



Each of the scientific steps in this process involves the application of the "scientific method".

Basic Science

- . Primarily NIH (National Institutes of Health), e.g., U.S. taxpayers
- . Driven by scientists submitting grant proposals
- . Generate a hypothesis; experiments may involve test tube, bacteria, yeast, animals, etc.

Preclinical testing

- . A candidate drug is identified in basic research
- . It is tested in an appropriate animal model; looking for efficacy and toxicity data
- . Mainly NIH funded

WHAT IS THE CLINICALS TRIALS PROCESS?

The answer to this question serves to clarify some of the fundamental misunderstandings and miscommunications about clinical trials between patients, physicians, hospital administrators, and third party payers.

There are many types of clinical trials and four (4) phases of clinical trials within each type. Thus, there are more than 24 different permutations of types and phases, making it very easy for one person to be describing "apples" and the other thinking the discussion is about "oranges".

WHAT ARE THE TYPES OF CLINICAL TRIALS?

- . Treatment
- . Prevention
- . Screening and early detection
- . Diagnostic
- . Genetic
- . Supportive care / Quality of life

More about the different types of trials in future essays.

WHAT ARE THE PHASES OF CLINICAL TRIALS?

- . Phase I
- . Phase II



- . Phase III
- . Phase IV

The process involves moving in an orderly manner, from Phase I through Phase IV, with different goals and issues at each Phase.

Phase I Clinical Trials:

- . Begins human testing of a drug that was promising in preclinical trials
- . Tested in a variety of cancer types
- . Determines a tolerable dose (to be used in future testing); follows plasma concentrations of the drug
- . Primarily assesses drug side-effects or toxicity
- . Typically involves 15 - 30 patients

Phase II Clinical Trials:

- . Takes a promising drug from Phase I trials
- . Tested in a specific type of cancer, to get an estimate of efficacy in that disease
- . Continue to gather information on toxicity
- . Typically involves less than 100 patients

Phase III Clinical Trials:

- . Takes an effective drug from Phase II trials and compares that new treatment to a current standard
- . Introduces the concept of randomization . some receive the new treatment, some receive the current standard
- . Continue to gather information on toxicity
- . Typically involves hundreds to thousands of patients

Phase "IV" (Post marketing) Clinical Trials:

- . Usually takes place after the drug is FDA-approved
- . Use to fine-tune dose and/or schedule of the drug Continue to gather information on toxicity
- . Continue to gather information on toxicity, especially long-term side-effects
- . May be a "repeat trial" to ensure the data can be replicated
- . Often run by Pharmaceutical companies
- . Typically involves hundreds to thousands of patients