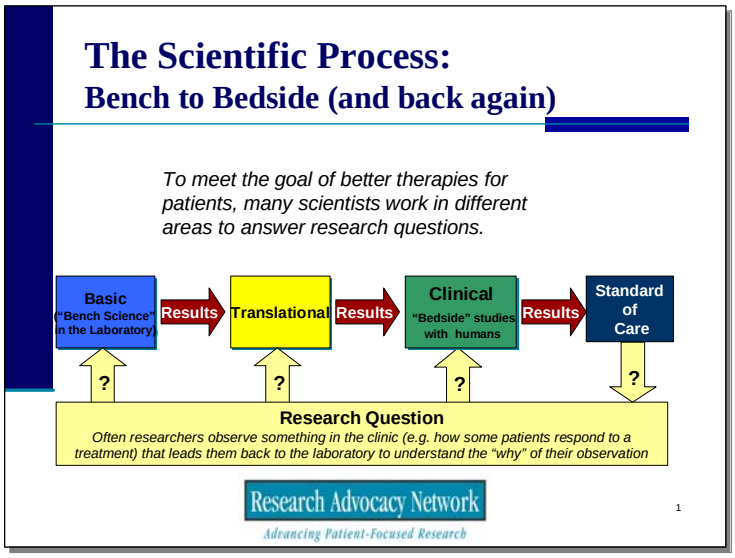
This shortcut sheet was developed by Research Advocacy Network to assist advocates in understanding how the results of basic, clinical and translational research concepts apply to clinical practice.

How Research Moves into Patient Care (Bench to Bedside)



Overview of the Clinical Trials System

What are clinical trials?

A clinical trial is one of the final stages of a long and careful cancer research process. They are research studies involving people and they try to answer specific scientific questions to find better ways to prevent, detect, or treat diseases or to improve care for people with diseases.

In cancer research, a clinical trial is designed to show how a certain anticancer approach, a promising drug, a new surgical procedure, a new diagnostic test, or a possible way to prevent cancer, affects the people who receive it.

Why Are Cancer Clinical Trials Important?

Most of the best cancer treatments we have today are based on what we learned from clinical trials. Cancer affects all of us and each year in the US more than half a million people are expected to die of cancer — more than 1,500 people a day. More than 1 million new cancer cases are expected to be diagnosed this year.

Why are there clinical trials?

Research on a specific drug starts with an idea about how that drug will work in people. The idea is then tested in a laboratory that focuses on basic research using cells and

animals. If the work with cells and animals supports the theory that a drug will work, clinical trials are designed to determine if the drug will work in humans.

Clinical trials translate results of basic scientific research into better ways to prevent, diagnose, or treat cancer.

Phases of Clinical Trials[1]

Clinical trials are conducted in a progressive series of steps called *phases*, each with distinct research goals. Progression to the next phase requires success related to the research goal with the benefits being greater than the risks they present to patients.

Phase I trials are conducted on treatments that appeared promising after extensive laboratory research, trials on animals, and the filing of an Investigational New Drug (IND) application with the FDA. The goal of this phase is to focus on determining the safety and side effects as well as the proper dose of these drugs. Only a small number of people are accepted for participation in these studies and they usually volunteer because other treatments are no longer effective.

Phase II trials are initiated to further investigate safety, dosages, and get a preliminary idea if the drug has a positive effect against the cancer. A slightly larger group of participants are involved since the new treatment was found to be reasonably safe in Phase I. Phase II trials are often the first treatment some patients receive. When promising results are found in Phase I and II, studies move to Phase III.

Phase III trials compare a new treatment with the best standard treatment and this is the final phase before FDA approval of a new treatment. Some people joining in this type of study are randomized (randomly chosen) to receive the new treatment plus standard treatment while others will get the standard treatment alone. The people who receive the standard treatment alone are referred to as the control group. The purpose of this type of trial is to determine if the new treatment is more beneficial than or adds any benefit to the standard therapy. Hundreds to thousands of people join in these studies if they are eligible.

Research Goals in Clinical Trials:

Phase I Is the drug safe?

Phase II Does the drug work?

Phase III How does the drug compare to standard care?

Phase IV – Post marketing requirement due to special circumstances approval process

1 Frankly Speaking About New Discoveries in Cancer : Introduction to New Discoveries in Cancer: How New Cancer Treatments are Developed and Tested http://www.thewellnesscommunity.org/programs/frankly/newdiscoveries/introduction/how.asp

Phase IV Sometimes these trials are required after FDA approval to confirm the agent's effect (especially to learn about complications or long-term toxicity) and to understand the drug's role in the disease. The number of patients included are all who take drug. The length of the study is defined in approval letter/protocol but must be complete in five years and demonstrate clinical benefits if involving the accelerated approval process. Phase IV trials may increase with FDA's use of accelerated approval.[2] For more information on accelerated approval and fast track please see the FDA website www.fda.gov or there is a chart detailing these in Cancer Research: A Guide to Clinical Trials, Module 3– Drug Development, Page 17.

Clinical Trial Monitoring

Clinical trials are developed to test a new drug, procedure or other therapy. The trial objectives are to:

- test for safety and efficacy
- determine which patients may benefit
- define the specific indications for use

Each clinical trial must have a protocol specifying how the trial will be conducted. Clinical trial monitoring ensures that the protocol is followed and participants are protected. Careful monitoring lets the researchers and sponsor learn about difficulties early and diminish the effect and minimize recurrences.

There are two types of clinical trial monitoring:

1. oversight of the quality of the trial
2. interim analysis

Oversight Of The Quality Of The Trial

Oversight of the quality of the trial includes:

- Protecting the rights and well-being of the participants
- Ensuring the trial is conducted according to the protocol. This adherence to predetermined methodology provides credibility to the process and the outcome.
- Accuracy, completeness and verifiability of the data being collected
- Adherence to good clinical practice and regulatory requirements
- Checking whether actual accrual is meeting projected targets
- Appropriateness of trial design assumptions

"It is the policy of the NIH (National Institutes of Health) that each Institute and Center (IC) should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-sponsored or conducted clinical trials."[1]

2 Cancer Research: A Guide to Clinical Trials, Coalition of National Cancer Cooperative Groups, Module 2 – Cancer Clinical Trials, page 20

National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) is responsible for overseeing the quality and monitoring programs used by the Cooperative Groups, Community Clinical Oncology Program (CCOP) Research Bases, and the Cancer Trials Support Unit (CTSU).

Their monitoring program covers:

- Accuracy of data submitted
- Verification of investigator compliance with protocol and regulatory requirements
- Provision of information on good clinical practice related to data collection and management

Food and Drug Administration (FDA)

The Food and Drug Administration (FDA) Good Clinical Practice Program provides guidance about clinical trial monitoring for clinical trials regulated by the FDA.

Institutional Review Board

The risk-benefit relationship in the clinical trial must be determined to be acceptable by an approved Institutional Review Board (IRB) before the trial can be conducted. The IRB monitors the progress of the study, adverse events, patient follow-up and withdrawals from the study.

It requires that the board have an understanding of the ability of the research staff to conduct ethical research that ensures race, gender, cultural sensitivity and community attitudes be respected.

Audit

"A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s)."[2]

Quality Assurance

"All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s)." [3]

Independent Data Monitoring Committee (IDMC), Data Safety Monitoring Board (DSMB)

For large, randomized, multi-site trials of treatments that intend to prolong life or reduce risk of a major adverse health outcome the comparisons of efficacy and safety should be the responsibility of an independent data monitoring committee (IDMC), data safety monitoring board (DSMB). These are formal committees that are external to the trial organizers and investigators and are distinct from the requirement for study review and approval by an Institutional Review Board (IRB).

The IDMC or DSMB protects the safety of the participants and the integrity of the trial by controlling access to trial information and analyzing data. While the sponsor appoints the committee or board, it does not control the deliberations. While sponsor representatives may sit on the committee or board, their roles must be clearly defined, including whether they have a vote or not. The responsibilities of the IDMC or DSMB should be clearly defined in the protocol. These responsibilities could include:

- regularly scheduled assessment of trial progress
- review of safety and efficacy data
- making recommendations regarding continuing, modifying or ending a trial
- patient recruitment
- patient follow-up/drop-out
- adverse events
- evidence of main effects

Interim Analysis

To prevent certain types of bias the protocol should specify what statistical analysis will be conducted and when it will be conducted. The unblinding (the key to which person was assigned to which arm) of the treatment assignments to those doing the analysis and the statistical analysis of the data is called interim analysis.

"An interim analysis is a scientific inferential process (i.e., estimation and hypothesis testing) for the purpose of making a decision(s) on whether or not to stop a clinical trial early for lack of intended effect or for overwhelming efficacy results in life-threatening and severely debilitating illness. It is different from the simple process of clinical trial monitoring which is concerned with scrutiny of a clinical trial to assure that the design assumptions (in the protocol) are reasonably met." [4]

Interim analysis is intended to compare efficacy and safety of the treatment arms. It is called interim because it is conducted before the formal completion of the trial. Interim analysis allows a trial to be closed early:

- if the treatment in one arm of the trial is clearly shown to be superior
- if it is unlikely that one treatment will be shown to be significantly different that another treatment in the same study
- if there are unacceptable adverse events

There must be stronger evidence to stop a trial early when the endpoint is efficacy than when the endpoint is safety. In a trial designed to look at both safety and efficacy, this multiplicity must be considered in the statistical planning for interim analysis.

The Food and Drug Administration (FDA) requests sponsors document considerations governing interim analysis in clinical trials. These considerations include:

- stated reasons for interim analysis
- planned number and times when interim analysis will occur
- stopping rules (see below)
- measures taken to minimize bias

Stopping Rules

Stopping rules can prevent over-reaction to random highs or lows in response or adverse event rates. Stopping rules or discontinuation guidelines by themselves are not enough to terminate a trial. The statistical computation done to determine whether to stop a trial must be taken in the context of new information, inaccuracy in assumptions and the limitations of any rule.

The DSMB uses sample size and statistical power considerations to detect a clinically meaningful difference in safety and/or efficacy between the treatment arms and make a decision whether to stop a trial early. Statistical calculations are used to make these determinations. Interim analysis is timed based on the number of patients involved and the events observed. Significance levels are determined using a number of methods. These methods include O'Brien Fleming, Haybittle-Peto, Pocock, Boniferrani. The method should be stated in the protocol.

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1 NIH Guide: NIH Policy for Data and Safety Monitoring, June 10, 1998

2 Guidance to Industry E6 Good Clinical Practice: Consolidated Guidance, April 1996

3 Guidance to Industry E6 Good Clinical Practice: Consolidated Guidance, April 1996

4 A. J. Sankoh, PhD, Interim Analyses: An Update of an FDA Reviewer's Experience and Perspective, Drug Information Journal, Vol. 33, pp. 165-176, 1999, p.167