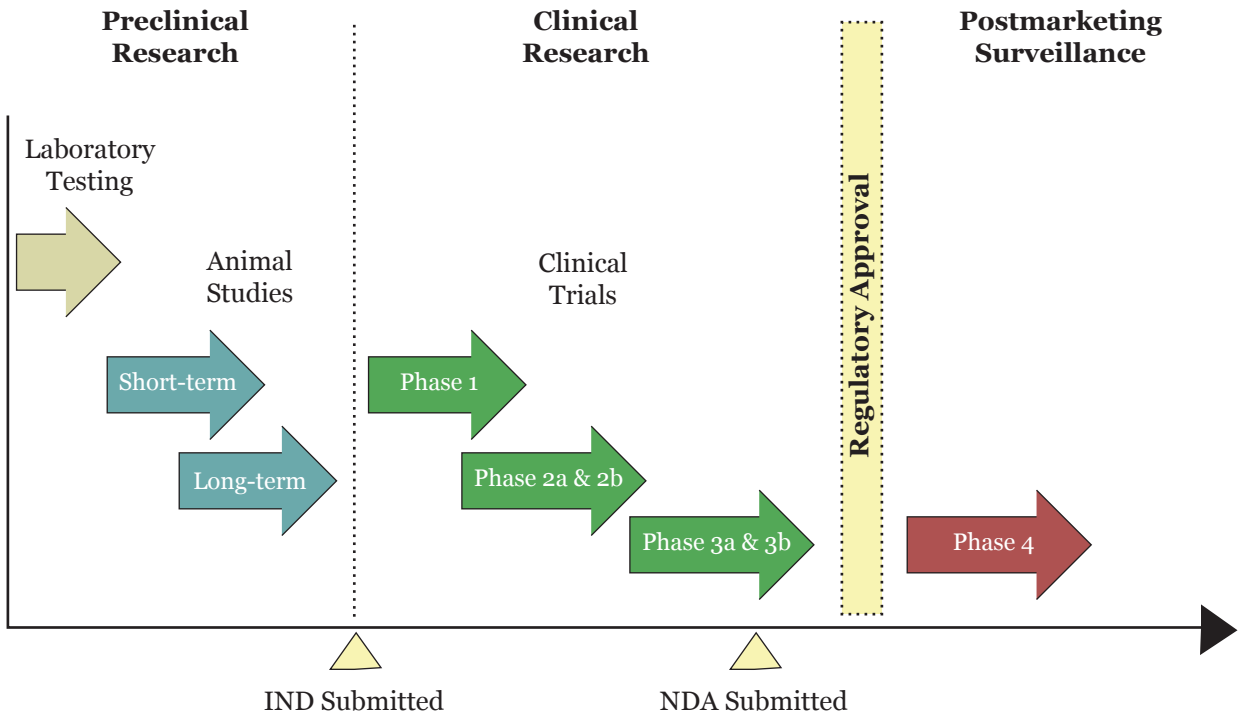
Not All Clinical Trials Are Created Equal – Understanding the Different Phases

This chapter will help you understand the differences between the various clinical trial phases and how these differences impact your responsibilities as a principal investigator.

Figure 1. Typical drug development schema



IND, investigational new drug application = request for authorization to test a new compound in humans from the US Food and Drug Administration (FDA); NDA, new drug application = request for marketing approval from the FDA.

The clinical development process for pharmaceutical agents is designed to provide the maximum information about a new investigational compound or intervention with the least risk to study subjects. Each clinical trial is performed to answer a specific research question, with the overarching purpose of improving patient care.

The origin of a new drug used to be serendipitous, with a random discovery that a natural compound had beneficial effects. As our knowledge about disease pathophysiology has expanded, the drug discovery process has become more targeted. However, most compounds that undergo identification, synthesis, characterization, and screening fail to show activity. For those few compounds that do demonstrate activity in vitro, preclinical (animal) studies are conducted to confirm the compound that showed promise actually has a beneficial effect on a living being. Preclinical studies also determine potential toxic effects at various doses and help to answer questions about drug absorption, metabolism, and elimination. Many compounds do not progress beyond the preclinical stage because they either fail to show any therapeutic activity or prove to be too harmful.

Clinical studies in humans begin after preclinical work has been completed. In the United States, before any studies in humans can begin, the drug sponsor must submit an investigational new drug (IND) application to the US Food and Drug Administration (FDA) for review. Because the FDA mandates that all drugs be approved before they can be transported or distributed across state lines, the IND is the formal process by which the study sponsor technically obtains exemption from this law

from the FDA. The purpose of the IND process is to ensure that humans will not be subjected to unreasonable risk.

Clinical trials are conducted in four phases also to ensure the safety of the study subjects. As development progresses through the phases (1–4), more patients are included and different questions are answered. Figure 1 provides an overview of the generic development process. Oftentimes, several studies of each phase are conducted, and the timing of the studies frequently overlaps (ie, Phase 3 studies are initiated before all of the Phase 2 studies are complete). Further discussion of each phase is presented below.

Clinical Trial Phases

Phase 1

Phase 1 trials represent the first time an experimental drug/treatment is tested in humans. The purpose of these trials is to define the treatment's safety, determine a safe dosage range, and explore the drug's metabolism, and pharmacokinetic and pharmacodynamic profile. Phase 1 studies are generally shorter in duration than subsequent phases. These trials are often conducted in the in-patient setting, so that effects can be carefully monitored. The tested range of doses will usually be a smaller percentage relative to body weight of the dose that caused harm in animal studies. During Phase 1, sufficient information must be obtained to allow the design of well-controlled Phase 2 studies.

Generally only a small group of subjects (20–80) is employed, and they are usually free of disease ("healthy"), so as not to confound the results. Patients with seriously impaired organ function (ie, kidney, liver, lung) may have less tolerance to the investigational compound, making it difficult to assess toxicity and increasing the risk of unacceptable side effects. For terminal conditions, such as cancer, however, patients with advanced disease may be included because they may not have other options. But, it has been estimated that only about 5% of participants in oncology Phase 1 trials clinically benefit from the study treatment.

Phase 1 studies are often designed such that small cohorts (3–6 patients) are administered different predefined dose levels. Doses are initially very low and based on the safety data from the preclinical studies. Different types of Phase 1 studies are conducted. One common initial study is the Single Ascending Dose study (SAD) where subjects are given a single dose of the drug for a set period of time. If no significant adverse effects are observed and the pharmacokinetic data are within predicted safe values, the dose is escalated, and a new cohort of subjects is then given the higher dose. This procedure is continued until a predetermined pharmacokinetic safety threshold is reached or intolerable side effects appear. This threshold is the maximum tolerated dose (MTD).

The Multiple Ascending Dose study (MAD) functions to define the pharmacokinetic and pharmacodynamic parameters of multiple doses of the investigational compound and often follows single dose Phase I studies. In these studies, multiple low doses of the drug are administered, and analyses are performed at various time points to understand how the drug is processed within the body. The dose is then subsequently escalated in another cohort of subjects up to a predetermined level.

An analysis of the effect of food on the pharmacokinetic profile of the investigational compound is another type of Phase 1 study. These studies are usually performed using a crossover design: subjects are given the compound at identical doses at 2 time points, when fasting and then after being fed a specified, often high-fat, meal.

Phase 2

Phase 2 trials are conducted in a larger group of subjects (100–300), who have a particular disease or condition, to determine the treatment's efficacy and further evaluate safety. Phase 2 studies are usually conducted at a limited number of sites. These studies are sometimes divided into Phase 2A and Phase 2B trials, where Phase 2A trials are specifically designed to assess dosing, and Phase 2B is specifically designed to determine efficacy.

Although subjects enrolled in Phase 2 trials have the target disease that the investigational compound is intended to treat, a relatively small and narrowly defined patient population is usually tested. The number of patients in Phase 2 trials is greater than that in Phase 1 studies because more patients are necessary to determine statistical significance, and because safety data in Phase 1 studies support the exposure of more subjects to the study agent.

Multiple doses and schedules are usually included in these trials. Most commonly, these are controlled studies where subjects are randomly assigned to receive multiple doses of the investigational compound or a comparator ("control"), which is usually placebo. For some disease states, an active control population might be used depending on the standard of care. An example would be psoriatic arthritis, where the effects of a biologic intervention plus a disease-modifying antirheumatic drug (DMARD) is tested against a DMARD-only group, where the standard of care ("active control") would be the DMARD. The end points are most often defined as the observed effects of treatment on symptoms or on some surrogate for what might be a more important clinical outcome.

Phase 3

In Phase 3 trials, the experimental drug/treatment is tested on a large group of subjects (1000–3000) with disease to confirm the treatment's efficacy, monitor side effects, compare it to commonly used therapies, and collect information that will allow the experimental treatment to be used safely. The study population is generally broader than the Phase 2 studies. Phase 3 trials are conducted at a large number of sites often across the country or in multiple countries. Sometimes these studies are differentiated into Phase 3A and Phase 3B trials, where 3A trials are performed before marketing approval, and 3B trials are supplemental to other trials (ie, longer-term information) or provide additional information (ie, effects on quality of life). Approval agencies (US Food and Drug Administration [FDA], European Medicines Agency [EMEA], Japan's Pharmaceuticals and Medical Devices Agency [PMDA]) prefer to have the results of two Phase 3 clinical trials before making a decision on the approval of an investigational compound. The data from Phase 3 trials are also used to expand the label of a marketed drug; for example in the case of a new indication or additional age group for which the product can be used.

These studies are randomized and controlled trials. Subjects are randomly assigned to receive either the investigational compound (generally fewer doses than Phase 2) or a comparator ("control"), which can be either placebo or the standard of care ("active control"). In general, fewer types of doses are tested in phase 3 studies as a consequence of the results obtained in phase 2. A large number of patients is sometimes required to detect a statistical difference between treatments.

Phase 4 (postmarketing)

After a drug has been approved by the regulatory agencies, research on the effects of the product continues. The term "postmarketing surveillance" is frequently used to describe studies conducted after a product is marketed. These studies are primarily observational or nonexperimental in nature, but

well-controlled Phase 4 studies can also be conducted.

The purpose of postmarketing studies (both observational and controlled) is to determine additional information such as the treatment's long-term risks, additional benefits, and optimal schedule, or to test the product in a broader population, such as children. Regulatory authorities may mandate these studies, or the sponsoring company may undertake them for competitive reasons or to test for interactions with other drugs in certain population groups, such as pregnant women, who are unlikely to subject themselves to clinical trials or to be a population studied in clinical trials.

Trial Phases Overview

	Phase 1	Phase 2	Phase 3	Phase 4
No. patients	20-80	100-300	1000-3000	Varies – generally >1000
No. sites	1	Limited	Many	Many*
Purpose	Define an agent's safety, determine a safe dosage range, and identify side effects	In a specific disease state, evaluate efficacy with a range of dose/frequency strategies, and further assess safety.	Confirm an agent's efficacy, monitor side effects, compare it to commonly used therapy, and collect additional safely information	Determine additional information such as the agent's long-term risks, additional benefits, and optimal schedule, or to test the product in different populations

**Surveillance studies may involve all practices where the agent is prescribed*

Types of Trials

In addition to differentiating clinical trials into phases, studies can be classified by the goal of the trial. Below is a brief description of each study type.

- Treatment trials test experimental therapies, new combinations of drugs, or new approaches to surgery or radiation therapy. An example of this type of trial is randomizing patients to an investigational topical psoriasis cream or placebo moisturizer and observing which intervention is associated with a better outcome after 2 weeks. Subjects in these trials have the disease or condition being investigated.

- Prevention trials determine better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. A study that examines the effect of a specific diet on the risk of myocardial infarction would be an example. Subjects in these trials do not have disease and may or may not have risk factors for the disease.

- Diagnostic trials investigate better tests or procedures for diagnosis of a particular disease or condition. An example would be a trial that compares the ability of a new type of x-ray machine to help in the diagnosis of osteoporosis versus standard x-ray equipment. Subjects in these trials often have risk factors or signs of the disease.

- Screening trials determine the best way to detect certain diseases or health conditions. This type of trial differs from a diagnostic trial in that a particular test or procedure is not being compared to another test or procedure; instead, a large population is studied to verify if a certain tool can detect a disease. An example of this type of trial is the use of a questionnaire administered to all of the students in the sixth grade in a local middle school to determine whether they have signs of depression. Subjects in these trials may or may not have the disease or condition, and patient status is determined in the context of conducting the study.

- Quality-of-life trials (supportive care) explore ways to improve comfort and quality of life for patients with chronic illness. An example of this type of trial includes a study that examines the effects of massage on cancer-related pain. Subjects in these trials have the disease or condition being investigated.

- Genetics studies focus on how genetic factors can influence the detection of disease or response to treatment, including side effects, and can be part of a treatment trial or a screening trial. For example, women may be tested for a gene thought to contribute to migraines; the prevalence of the gene in women who suffer from migraines is compared to those who do not to determine if a link can be established. Another example would be a trial of Parkinson's disease patients where the effects of a drug in patients with a certain genetic mutation are compared to the effects of the drug in those without the mutation, to determine if one group of patients responds better. The population enrolled in these trials depends on the goal of the study; for the first example, both subjects who have the disease and those that do not would be included, while in the second example, all subjects would have the particular disease.

Overview of types of trials

	Treatment	Prevention	Diagnostic	Screening	Quality of life	Genetics
Purpose	Test experimental therapies, new combinations of drugs, or new approaches to treatment	Determine better ways to prevent disease in people who have never had the disease or to prevent a disease from returning	Investigate better tests or procedures for diagnosis of a particular disease or condition	Determine the best way to detect certain diseases or health conditions	Explore ways to improve comfort and quality of life for patients with chronic illness	Focus on how genetic factors can influence the detection of disease or response to treatment
Patient population	With disease	Without disease	With risk factors or signs of disease	With and without disease	With disease	With or without disease*

**Depends on goal of the study*

Resources

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