Chapter 12
The Phases of Clinical Studies

12.1 Introduction

The phases of clinical research are the steps of scientists' experiments during a health intervention in an attempt to find enough evidence for a process that would be useful as a medical treatment. In the case of a pharmaceutical study, the phases start with drug design and drug discovery, go on to animal testing, then start by testing in only a few human subjects and expand to test in many more study participants if the trial seems safe and useful [1].

Clinical trials involving new drugs are commonly classified into four phases. Clinical trials of drugs may not fit into a single phase. For example, some may blend from phase I to phase II or from phase II to phase III. Therefore, it may be easier to think of early-phase studies and late-phase studies [2]. The drug development process will normally proceed through all four phases over many years. If the drug successfully passes through phases I, II and III, it will usually be approved by the national regulatory authority for use in the general population. Phase-IV studies are 'post-approval' [1].

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12.2 Preclinical Studies

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive preclinical studies. These involve in vitro (test tube or cell culture) and in vivo (animal) experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information. Such tests assist pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug [1].

12.3 Phase 0

Phase-0 trials are the first clinical trials among people. They aim to learn how a drug is processed in the body and how it affects the body. In these trials, a very small dose of a drug is given to about 10–15 people [3].

'Phase 0 trials are also known as human micro dosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as expected from preclinical studies. Distinctive features of phase-0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (what the body does to the drugs)' [4].

A phase-0 study gives no data on safety or efficacy being, by definition, a dose too low to cause any therapeutic effect. Drug development companies carry out phase-0 studies to rank drug candidates to take forwards into further development on the basis of which has the best pharmacokinetic parameters in humans. They enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data [1].

12.4 Phase I

Phase-I trials aim to find the best dose of a new drug with the fewest side effects. The drug will be tested in a small group of 15–30 patients. Doctors start by giving very low doses of the drug to a few patients. Higher doses are given to other patients until side effects become too severe or the desired effect is seen. The drug may help patients, but phase-I trials are to test a drug's safety. If a drug is found to be safe enough, it can be tested in a phase-II clinical trial [3].

Initial Safety Trials on a New Medicine 'An attempt is made to establish the dose range tolerated by volunteers for single and multiple doses. Phase-I trials are sometimes conducted in severely ill patients (e.g. in the field of cancer) or in less ill patients when pharmacokinetic issues are addressed (e.g. metabolism of a new antiepileptic medicine in stable epileptic patients whose microsomal liver enzymes have been induced by other antiepileptic medicines). Pharmacokinetic trials are usually considered phase-I trials regardless of when they are conducted during a medicine's development' [5, 6].

Phase-I trials are the first stage of testing in human subjects. Normally, a small group of 20–100 healthy volunteers will be recruited. This phase is designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics and pharmacodynamics of a drug. These trials are often conducted in a clinical trial clinic, where the subject can be observed by full-time staff. These clinical trial clinics are often run by contract research organisations (CROs), who conduct these studies on behalf of pharmaceutical companies or other research investigators. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase-I trials also normally include dose ranging, also called dose-escalation studies, so that the best and safest dose can be found and to discover the point at which a compound is too poisonous to administer [7].

Phase Ia (Single Ascending Dose) In single ascending dose studies, small groups of subjects are given a single dose of the drug, while they are observed and tested for a period to confirm safety [1, 8] Typically, a small number of participants, usually three, are entered sequentially at a particular dose [2]. If they do not exhibit any adverse side effects, and the pharmacokinetic data are roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. If unacceptable toxicity is observed in any of the three participants, an additional number of participants, usually three, are treated at the same dose [1, 2].

Phase Ib (Multiple Ascending Dose) Multiple ascending dose studies investigate the pharmacokinetics and pharmacodynamics of multiple doses of a drug, looking at safety and tolerability. In these studies, a group of patients receives multiple low doses of the drug, while samples (of blood and other fluids) are collected at various time points and analysed to acquire information on how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level [1, 8].

12.5 Phase II

Phase-II trials further assess safety as well as whether a drug works. The drug is often tested among patients with a specific type of cancer. Phase-II trials are performed in larger groups of patients compared to phase-I trials. Often, new combinations of drugs are tested. Patients are closely watched to see if the drug works. However, the new drug is rarely compared to the current (standard-of-care) drug that is used. If a drug is found to work, it can be tested in a phase-III clinical trial [3].

Once a dose or range of doses has been determined, the next goal is to evaluate whether the drug has any biological activity or effect [2]. Phase-II trials are performed on larger groups

(100–300) and are designed to assess how well the drug works, as well as to continue phase-I safety assessments in a larger group of volunteers and patients. Genetic testing is common, particularly when there is evidence of variation in metabolic rates [2]. When the development process for a new drug fails, this usually occurs during phase-II trials, when the drug is discovered not to work as planned or to have toxic effects [1].

'Phase-II studies are sometimes divided into phase IIA and phase IIB' [1].

- 'Phase IIA is specifically designed to assess dosing requirements (how much drug should be given)'.
- 'Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s))'.

Some trials combine phase I and phase II and test both efficacy and toxicity [1].

Phase IIa 'Pilot clinical trials to evaluate efficacy (and safety) in selected populations of patients with the disease or condition to be treated, diagnosed, or prevented. Objectives may focus on dose–response, type of patient, frequency of dosing, or numerous other characteristics of safety and efficacy' [5, 6].

Phase IIb 'Well-controlled trials to evaluate efficacy (and safety) in patients with the disease or condition to be treated, diagnosed, or prevented. These clinical trials usually represent the most rigorous demonstration of a medicine's efficacy. Sometimes referred to as pivotal trials' [5, 6].

12.6 Phase III

This phase is designed to assess the effectiveness of a new intervention and, thereby, its value in clinical practice [1, 2]. 'Phase-III studies are randomised controlled multicenter trials on large patient

groups (300–3000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective a drug is, in comparison with the current "gold standard" treatment. Because of their size and comparatively long duration, phase-III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions'. Phase-III trials of chronic conditions or diseases often have a short follow-up period for evaluation, relative to the period of time the intervention might be used in practice [2]. This is sometimes called the 'premarketing phase' because it actually measures consumer response to the drug [1].

Phase-III trials compare a new drug to the standard-of-care drug. These trials assess the side effects of each drug and which drug works better. Phase-III trials enrol 100 or more patients.

Often, these trials are randomised. This means that patients are put into a treatment group, called trial arms, by chance. Randomisation is needed to make sure that the people in all trial arms are alike. This lets scientists know that the results of the clinical trial are due to the treatment and not to differences between the groups. A computer programme is often used to randomly assign people to the trial arms [3].

There can be more than two treatment groups in phase-III trials. The control group gets the standard-of-care treatment. The other groups get a new treatment. Neither a patient nor the patient's doctor can choose the group. The patient will also not know which group he/she is in until the trial is over.

Every patient in a phase-III study is watched closely. The study will be stopped early if the side effects of the new drug are too severe or if one group has much better results. Phase-III clinical trials are often needed before the FDA will approve the use of a new drug for the general public [3].

Phase IIIa Trials conducted after the efficacy of a medicine is demonstrated, but prior to regulatory submission of an NDA or other dossiers. These clinical trials are conducted in patient

populations for whom the medicine is eventually intended. Phase-IIIa clinical trials generate additional data on both safety and efficacy in relatively large numbers of patients in both controlled and uncontrolled trials. Clinical trials are also conducted in special groups of patients (e.g. renal failure patients) or under special conditions dictated by the nature of the medicine and the disease. These trials often provide much of the information needed for the package insert and labelling of the medicine [5, 6].

Phase IIIb Clinical trials conducted after regulatory submission of an NDA or other dossier, but prior to the medicine's approval and launch. These trials may supplement earlier trials, may complete earlier trials or may be directed towards new types of trials (e.g. quality of life, marketing) or phase-IV evaluations. This is the period between submission and approval of a regulatory dossier for marketing authorisation [3, 5].

12.7 Phase IV

'A phase-IV trial is also known as a postmarketing surveillance trial. Phase-IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold (e.g. after approval under the FDA Accelerated Approval Program). Phase-IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer period than was possible during the phase-I to phase-III clinical trials' [1].

Phase-IV trials test new drugs approved by the FDA. The drug is tested in several hundreds or thousands of patients. This allows for better research on short-lived and long-lasting side effects and safety. For instance, some rare side effects may be found only in large groups of people. Doctors can also learn more about how well the drug works and whether it is helpful when used with other treatments [3].

Studies or Trials Conducted After a Medicine is Marketed to Provide Additional Details About the Medicine's Efficacy or Safety Profile Different formulations, dosages, durations of treatment, medicine interactions and other medicine comparisons may be evaluated. New age groups, races and other types of patients can be studied. Detection and definition of previously unknown or inadequately quantified adverse reactions and related risk factors are an important aspect of many phase-IV studies. If a marketed medicine is to be evaluated for another (i.e. new) indication, then those clinical trials are considered phase-II clinical trials. The term postmarketing surveillance is frequently used to describe those clinical studies in phase IV (i.e. the period following marketing) that are primarily observational or non-experimental in nature, to distinguish them from well-controlled phase-IV clinical trials or marketing studies [5, 6].

12.8 Summary of Clinical Trial Phases

Preclinical

Primary goal: Testing of a drug in non-human subjects, to gather efficacy, toxicity and pharmacokinetic information

Dose: Unrestricted

Patient monitor: A graduate-level researcher (Ph.D.)

Typical number of participants: Not applicable (in vitro and in vivo only) [1]

Phase 0
Primary goal: Pharmacodynamics and pharmacokinetics, particularly oral bioavailability and half-life of the drug
Dose: Very small, subtherapeutic
Patient monitor: Clinical researcher
Typical number of participants: Ten people
Notes: Often skipped for phase I [1]

Phase I
Primary goal: Testing of drug on healthy volunteers for dose ranging
Dose: Often subtherapeutic, but with ascending doses
Patient monitor: Clinical researcher
Typical number of participants: 20–100 people
Notes: Determines whether a drug is safe to check for efficacy [1]

Phase II
Primary goal: Testing of a drug on patients to assess efficacy and safety
Dose: Therapeutic dose
Patient monitor: Clinical researcher
Typical number of participants: 100–300 people
Notes: Determines whether a drug can have any efficacy; at this point, the drug is not presumed to have any therapeutic effect whatsoever [1].

Phase III
Primary goal: Testing of a drug on patients to assess efficacy, effectiveness and safety
Dose: Therapeutic dose

Patient monitor: Clinical researcher and personal physician

Typical number of participants: 1000–2000 people

Notes: Determines a drug's therapeutic effect; at this point, the drug is presumed to have some effect [1]

Phase VI

Primary goal: Postmarketing surveillance – watching drug use among the public

Dose: Therapeutic dose

Patient monitor: Personal physician

Typical number of participants: Anyone seeking treatment from their physician

Notes: To watch drug's long-term effects [1]

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