Chapter 5
Clinical Phases of Device and Drug Evaluation with Emphasis on Early Phase Trials

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Overview of Regulatory Phases for Investigational Agents

The US Food and Drug Administration and regulatory agencies in other parts of the world follow a measured sequential approach to the testing of investigational agents that emphasizes safety. Ultimately an agent must be shown to be both safe and effective before it receives marketing approval. However, at the initial stages of clinical research on the product, studies are generally small with a primary focus on identifying large safety signals. As data are accumulated, later phases of clinical investigation involve larger numbers of study participants where the focus on safety continues through more refined assessments of subtler safety signals with increasing emphasis on establishing efficacy.

The basic regulatory phases (I–IV) for drug development were developed first and are well known. The more recent guidelines for vaccines and biologics use the same structure. Device approval guidelines use a different sequential approach to device evaluation. The following table gives an overview of the regulatory phases for drugs, vaccines, biologics and devices (see Table 5.1).

Regulatory Phases for Device Approval

The Food and Drug Administration Center for Devices and Radiological Health is responsible for the review of marketing applications for devices in the USA. The phases of device evaluation and regulatory approval differ from those for drugs and include feasibility and pivotal trials.

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Table 5.1 Regulatory phases for assessment of investigational agents

	Drugs, vaccines, biologics	Devices
Early	Phase I (includes Phase 0 and proof of concept)	Feasibility (includes proof of concept)
Middle	Phase II (includes Phase IIa and IIb)	Feasibility
Late	Phase III Phase IV	Pivotal

FDA classifies devices based on their level of risk and intended use. Class I devices are deemed to be low risk and are therefore subject to the least regulatory controls. For example, surgical instruments are generally classified as Class I devices. Class II devices are higher-risk devices than Class I and require greater regulatory controls to provide reasonable assurance of the device's safety and effectiveness. For example, contact lenses and ultrasound devices are classified as Class II devices. Class III devices are generally the highest-risk devices and are therefore subject to the highest level of regulatory control. Class III devices must typically be approved by FDA before they are marketed. Class III devices are life-supporting, life-sustaining or important in preventing impairment of human health. For example, replacement heart valves are classified as Class III devices [1].

Class III devices must go through a premarket approval process that involves two stages of clinical studies, feasibility studies and a pivotal trial.

Feasibility Study

A feasibility study may provide support for a future pivotal study or may be used to answer basic research questions about the device. It is often required by FDA prior to the pivotal study to assess basic safety and potential for effectiveness. The sample sizes for these studies are generally between 10 and 40, although they can be larger. Ultimately, the decision to proceed to the next phase of clinical evaluation is based on whether the potential benefit from the device justifies the risk.

Pivotal Study

The pivotal study is the definitive trial assessing the safety and efficacy of the device that will be used to obtain marketing approval. Device trials tend to be smaller than drug trials. Many are difficult to blind, and safety and effectiveness may depend on physician technique. Data from the pivotal study will be used as the primary clinical support for a marketing application. This stage of clinical study must provide a "reasonable assurance of safety and effectiveness" for the marketing application.

Regulatory Phases for Trials of Drugs, Vaccines and Biologics

The International Conference for Harmonization has defined three phases of clinical studies that are required to move a drug out of preclinical testing into clinical testing and ultimately to marketing approval [2]. The FDA Center for Drug Evaluation and Research (CDER) and the FDA Center for Biologics Evaluation and Research (CBER) use the same classification system for drugs, vaccines and biologics.

Phase 0 Trials

In 2007, FDA issued guidance on exploratory INDs [3]. An exploratory IND study is intended to describe a clinical trial that is conducted early in Phase I, involves very limited human exposure, and has no therapeutic or diagnostic intent (e.g., screening studies, microdose studies). Such exploratory IND studies are conducted prior to the traditional Phase I dose escalation, safety and tolerance studies that ordinarily initiate a clinical drug development program. The duration of dosing in an exploratory IND study is expected to be limited. Exploratory IND studies are identified as Phase 0 trials [4].

The FDA Exploratory IND Guidance includes examples of three types of Phase 0 trials: determination of biodistribution, determination of pharmacokinetics and bioavailability, and evaluation of the mechanism(s) of drug action. These trials provide an opportunity to examine a new agent in humans earlier than traditional dose-finding, toxicity-driven Phase I trials. Because a limited number of subtherapeutic doses are administered in the Phase 0 setting, assessment of preclinical toxicology can also be limited before proceeding to Phase I. Thus, Phase 0 trials permit identification of potential therapeutic failures earlier in the drug development process. Only drugs showing sufficient promise are to be evaluated for safety and tolerability in traditional Phase I trials.

For Phase 0 trials, a single dose or a short course (typically fewer than seven days) of low, non-therapeutic, non-toxic doses is administered to a few patients. PK/PD studies are conducted on these patients. It is essential that the drugs being considered for a Phase 0 trial have a high therapeutic ratio in preclinical toxicity models in vivo so that the desired PK or PD effect may be observed without substantial toxicity. Potential cancer chemopreventive agents may be suitable for evaluation in a Phase 0 trial.

Phase I Clinical Studies

Following completion of preclinical testing, trials that involve the initial administration of a drug, vaccine or biologic in humans are identified as Phase I clinical studies. Studies in this phase of development usually have non-therapeutic objectives as their primary intent, although the data from these studies are also used to provide very preliminary data on potential effectiveness. These studies are closely monitored and may be conducted in patients with the medical condition for which the drug may have potential use, e.g., patients with mild hypertension, but are usually conducted in healthy volunteer subjects. Drugs with significant potential toxicity, e.g., cytotoxic drugs, are usually studied in patients with the medical condition of interest.

Phase I trials are often non-randomized and do not employ a control group. However, many designs involve initial assessments of a range of doses for the agent that can include very low subtherapeutic doses. Sample sizes for Phase I are usually between 20 and 100. Studies conducted in Phase I typically involve one or a combination of the following aspects:

Estimation of Initial Safety and Tolerability

The initial evaluation of an investigational new drug in humans is usually intended to determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. Depending on the nature of the investigational agent, these studies typically may include single- or multiple-dose administration. Determination of dose-limiting toxicity, and the maximum tolerated dose are primary goals of Phase I trials.

Although Phase I trials were originally conceived as the first test of safety in humans, Phase I trial designs and objectives evolved over time to maximize information obtained from this early phase of drug development to guide the next phases of clinical research for the drug. Thus, these trials are also used to assess mechanism of action and early evidence of effectiveness.

Pharmacokinetics/Pharmacodynamics (PK/PD)

The preliminary characterization of the pharmacokinetics of a drug is an important goal of Phase I. Pharmacokinetics (PK) is defined as the study of the time course of drug absorption, distribution, metabolism and excretion. PK may be assessed via separate studies or as a part of efficacy, safety and tolerance studies. PK studies are particularly important to assess the clearance of the drug, possible accumulation of

parent drug or metabolites and potential drug–drug interactions. Although drug–drug interaction studies are generally performed in phases beyond Phase I, animal and in vitro studies of metabolism and potential interactions may lead to doing drug–drug interaction studies earlier.

Pharmacodynamics (PD) studies assess the mechanisms of action of drugs and other biochemical and physiological effects on tissues and organ systems. PD data can provide early estimates of activity and potential efficacy and may guide the dosage and dose regimen in later studies.

PK/PD studies may be conducted in healthy volunteer subjects or in patients with the target disease. Designs for these studies typically involve taking serial measurements from test subjects after dose administration.

Early Measurement of Drug Activity

Preliminary studies of potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

Phase I Trial Designs

There are a wide range of Phase I designs [5]. One of the most frequently used designs is the "3 + 3" design, which is one of the simpler forms of a dose escalation design [6]. A group of three test subjects is treated at a starting dose that is considered to be safe based on extrapolation from animal toxicological data. If none of the three subjects in a cohort experiences a dose-limiting toxicity, another three subjects will be treated at the next higher dose level. However, if one of the first three subjects experiences a dose-limiting toxicity, three more subjects will be treated at the same dose level. If no more than one of the six experiences a dose-limiting toxicity, then the trial proceeds to the next dose level in three new test subjects. The dose escalation continues until at least two subjects tested at a dose level experience dose-limiting toxicities. The recommended dose for Phase II trials is conventionally defined as the dose level just below this toxic dose level.

Not all Phase I designs involve evaluation of various doses of a treatment. Siprashvili et al. conducted a single-center Phase I clinical trial to evaluate the safety and wound outcomes following genetically corrected autologous epidermal grafts in 4 patients with recessive dystrophic epidermolysis bullosa (RDEB), an inherited blistering disorder caused by mutations in the COL7A1 gene encoding type VII collagen. RDEB causes significant disability and is often fatal. Autologous keratinocytes isolated from biopsy samples collected from the patients were transduced with retrovirus carrying full-length human COL7A1 and assembled into

epidermal sheet grafts. Type VII collagen gene-corrected grafts were transplanted onto 6 wounds in each of the patients. The primary safety outcomes were recombination competent retrovirus, cancer and autoimmune reaction. Through one year of observation, all grafts were well tolerated without serious adverse events. No clinical signs of malignancy were observed. Recombinant retrovirus and cytotoxic T-cell assays were negative for the majority of time points; a minority was undetermined. Wound healing was assessed using serial photographs taken at 3, 6 and 12 months after grafting. Wound healing was observed in some type VII collagen gene-corrected grafts, but the response was variable among patients and among grafted sites and generally declined over 1 year [7].

Phase II Clinical Studies

Phase II includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase II studies are typically well controlled, closely monitored and conducted in a relatively small number of patients, usually involving several hundred people.

A series of Phase II trials may be conducted before a decision to proceed to a Phase III clinical study is made. Phase II is usually considered to start with the initiation of studies in which the primary objective is to explore therapeutic efficacy in patients.

Phase IIa Studies

Early Phase II clinical studies are identified as Phase IIa studies. These are generally exploratory with a primary objective of evaluating clinical efficacy, pharmacodynamics or biological activity. These may be conducted in healthy volunteers or in patients with the target medical condition. Phase IIa trials may be non-randomized, using historic or concurrent controls or a pre-post design where test subjects serve as their own control.

Late Phase II clinical studies, known as Phase IIb, are dose range finding studies in patients with efficacy as the primary endpoint. Phase IIb trials are usually randomized and concurrently controlled to evaluate the efficacy of the drug and its safety for a particular therapeutic indication. Studies in Phase IIb are typically conducted in a group of patients who are selected by relatively narrow criteria, leading to a relatively homogeneous population and are closely monitored.

An important goal for this phase is to determine the dose regimen for Phase III trials, including dose range and frequency and timing of administration. Early studies in this phase often utilize dose escalation designs to give an early estimate of

dose–response, and later studies may confirm the dose–response relationship for the indication in question by using parallel dose–response designs. Confirmatory dose–response studies may be conducted in Phase II or left for Phase III. Doses used in Phase II are usually but not always less than the highest doses used in Phase I.

Proof of Concept Studies

Proof of Concept (Proof of Principle) studies are an early stage of clinical drug development when a compound has shown potential in animal models and early safety testing. This step of proof of principle or proof of concept often links between Phase I and dose ranging Phase II studies. Thus, a Proof of Concept (POC) study can be thought of as a type of Phase IIa trial. Cartwright et al. describe a proof of concept study as "the earliest point in the drug development process at which the weight of evidence suggests that it is 'reasonably likely' that the key attributes for success are present and the key causes of failure are absent… Tools for POC include biomarkers, targeted populations, pharmacokinetic (PK)/pharmacodynamic (PD) modeling, simulation, and adaptive study designs" [8].

These small-scale studies are designed to detect a signal that the drug is active on a pathophysiologically relevant mechanism, as well as preliminary evidence of efficacy in a clinically relevant endpoint. Sponsors use these studies to estimate whether their compound might have clinically significant efficacy in other diseases states as well. For example, a drug with potential therapeutic efficacy for treatment of epilepsy may also be evaluated for its ability to treat other conditions (e.g., migraine, neuropathic pain, anxiety, depression) [9].

Example

Cartright et al. [8] provide an example of a proof of concept trial which was conducted by Lachmann et al. [10]. ACZ885, a monoclonal antibody against interleukin 1β, was administered to four patients with Muckle–Wells syndrome, an autoimmune disease in which interleukin-1 has a central role. In these four patients, a single-intravenous injection resulted in complete clinical remission within 8 days, with biomarkers of inflammation returning to normal ranges over the same time period. Because the antibody performed as designed, the proof of concept was demonstrated.

Phase IIb Studies

Phase IIb studies can be used as pivotal trials, if the drug is intended to treat life-threatening or severely debilitating illnesses as in oncology indications [11].

Additional objectives of clinical trials conducted in Phase II may include evaluation of potential study endpoints, concomitant medications and target populations (e.g., mild versus severe disease) for further study in Phase II or III. These objectives may be accomplished employing exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

Phase II Trial Designs

Although many Phase II designs are non-randomized, many efficient randomized clinical trial designs have emerged and randomized Phase II designs are becoming more common [12]. There are three categories of randomized Phase II designs: (1) randomization to parallel non-comparative single-arm experimental regimens where the decision whether a single-arm shows evidence of efficacy is independent of the data from the other arms; (2) randomized selection (or pick the winner) designs for selecting the most promising experimental regimen among several similar experimental regimens [13, 14]; and (3) randomized screening design for comparing an experimental regimen to standard of care [15].

Phase III Clinical Studies

Phase III studies are larger trials that usually include a control group and random treatment assignment to the investigational agent or control. They are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit–risk relationship of the drug. Phase III studies also provide a basis for extrapolating the results to the general population. Phase III studies usually include several hundred to several thousand participants.

Phase III begins with the initiation of studies in which the primary objective is to demonstrate, or confirm therapeutic benefit. Studies in Phase III are designed to confirm the preliminary evidence from Phase II that a drug is safe and effective for use in the intended indication and target population. These studies are intended to provide the basis for marketing approval. Studies in Phase III may also further explore the dose–response relationship or explore the drug's use in wider populations, in different stages of disease, or in combination with another drug. For drugs intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III.

A trial designed and executed to obtain statistically significant evidence of efficacy and safety as required for marketing approval by regulatory agencies such as FDA is identified as a Phase IIIa trial. A Phase IIIB is a study started prior to approval and whose primary intention is support of publications rather than registration or label changes. The results are not intended to be included in the submission dossier.

Procedural Trials

Trials of a procedural technique do not fall under the purview of regulatory agency review before the technique can be used in general surgical practice. Thus, a new surgical technique or refinement of an existing technique can move from use by a few expert surgical practices that were instrumental in developing the technique to more widespread use without class I evidence to assess the benefit:risk ratio of the new technique.

For example, laparoscopic cholecystectomy moved into widespread use in the early 1990s without rigorous evidence from a randomized clinical trial comparing it to open cholecystectomy. Rather, its widespread adoption was driven by observational data indicating its safety and effectiveness and patient preference for a less invasive procedure, which quickly moved use of the technique from a few specialty centers to widespread use in general surgical practice [16–18].

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